# A prospective, cross-over randomized controlled trial to determine whether end stage renal disease patients receiving chronic renal replacement therapy at Charlotte Maxeke Johannesburg Academic Hospital are more likely to have an improved lipid profile after including plant sterols as part of their dietary intake for eight weeks

by
Nicole Pereira Ribeiro

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Supervisor: Dr. S Potgieter
Co-supervisor: Prof. S Naicker
Statistician: Prof. DG Nel

Faculty of Medicine and Health Sciences
Department of Interdisciplinary Health Sciences
Division of Human Nutrition

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## DECLARATION

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Nicole Pereira Ribeiro

## ABSTRACT

**INTRODUCTION:** Dyslipidemia, specifically raised total cholesterol and low density lipoprotein (LDL) cholesterol levels, is very common amongst end stage renal disease (ESRD) patients. The cholesterol-lowering effectiveness of plant sterol therapy as recommended by the various guidelines for treating dyslipidemia in ESRD patients receiving renal replacement therapy (RRT), has not been fully tested in this population group. The aim of this study was to assess whether ESRD patients receiving RRT at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) are more likely to improve lipid profiles during eight weeks of including plant sterols as part of their dietary recommendations.

**METHODS:** Adult hemodialysis (HD) and peritoneal dialysis (PD) patients attending CMJAH who met the inclusion criteria were included in the study. The 20 week trial was a randomised, double-blind, prospective cross-over trial - whereby the primary researcher, randomly selected two groups based on HD or PD treatment modality being received to either receive 'Tub A' (test: Floro Proactive, Unilever, South Africa) or 'Tub B' (control: Floro extra light). Weight, height, body mass index (BMI) and waist circumference (WC, where applicable) were measured, lipograms and activity levels were evaluated, dietary assessments were completed using 24-hour recall.

**RESULTS:** Of the 89 patients who signed informed consent, only 73 completed the trial, this was controlled for those who consumed the specified 25g per day further reducing the number of participants evaluated to 49 (n=27 and n=22 for PD and HD participants' respectively). The mean age was 39±10.5 and 42±12.2 years for PD and HD respectively and the mean duration of RRT was 6 years for HD (range 1-16 years) and 4 years for PD (range 1-10 years). The most of the HD and PD participants had a normal BMI, and most of the HD participants had a normal waist circumference. Majority of the participants were classified as moderately active. The mean dietary requirements for cardioprotective effects as recommended by the guidelines were not adequately met for PD and HD groups respectively in terms of protein 81% (78-81%) and 73% (73-74%) protein per ideal body weight) respectively and total energy 88% (78-92%) and 72% (72-75%) total energy per ideal body weight), and fat 82% (78-82%) and 113% (112-113%) total fat, 101% (98-101%) and 111% (111-112%) saturated fat, 117% (104-117%) and 131% (131-136%) polyunsaturated fat, and 41% (39-41%) and 43% (43-45%) monounsaturated fat) and carbohydrates 107% (106-107%) and 90% (90-92%) for percentage carbohydrate intake with 58% (58-60%) and 67% (67-71%) of the required fibre. The average total-cholesterol, LDL-cholesterol, HDL-cholesterol and triglyceride levels at baseline of participants were 4.79±1.39 mmol/l and 3.51±0.79 mmol/l; 3.00±1.07 mmol/l and 1.95±0.64 mmol/l;

0.99±0.33 mmol/l and 1.06±0.05 mmol/l; and 1.74±0.94 mmol/l and 1.07±0.49 mmol/l for PD and HD participants respectively. There was no statistically significant association between total-cholesterol, LDL-cholesterol, HDL-cholesterol and triglyceride levels of participants and the appropriate use of the respective margarines (test versus control). In turn the test margarine had a non-significant positive association with reduced total cholesterol (p=0.66 and p=0.16) and LDL cholesterol (p=0.89 and p=0.57) in ESRD patients receiving PD or HD respectively. Body mass index, waist circumference, activity level and extent of dietary compliance in accordance to the guidelines did not play a significant role in the change in total-cholesterol and LDL-cholesterol levels of participants.

**DISCUSSION:** Overall dietary assessment illustrated that their habitual intake was not appropriate for cardioprotective effects regarding fibre and fat. This could have decreased the efficacy of the sterol-enriched margarine when incorporated into their habitual dietary intake, and resulted in a decrease in HDL cholesterol levels. ESRD patients may be hyper-responders, as the inclusion of the phytosterol-enriched margarine did show a trend towards decreasing both total and LDL cholesterol levels, even though not statistically significant.

# OPSOMMING

**INLEIDING:** Dislipidemie, of meer spesifiek verhoogde totale cholesterol en lae digtheid lipoproteïen (LDL) cholesterol vlakke is baie algemeen by pasiënte wat presenteer met eindstadium nierversaking (ESNV). Die effek van die insluiting van cholesterol-verlagende plantsterole, soos aanbeveel deur verskeie riglyne vir die behandeling van dislipidemie in ESNV pasiënte wat dialise ontvang, is nie ten volle getoets in hierdie studiepopulasie nie. Die doel van hierdie studie was om te bepaal of ESNV pasiënte wat dialise by Charlotte Maxeke Akademiese Hospitaal in Johannesburg (CMJAH) ontvang, meer geneig is om verbeterde lipiedprofiele te toon nadat plantsterole vir agt weke as deel van hulle dieetinname ingesluit is.

**METODES:** Volwasse hemodialise (HD) en peritoneale dialise (PD) pasiënte wat behandeling ontvang by CMJAH en wat aan die insluitingskriteria voldoen het, is ingesluit in die studie. Die 20 weke studie was 'n ewekansig geselekteerde, dubbel blinde, oorkruis kliniese prospektiewe studie. Die primêre navorser het twee groepe ewekansig gekies, gebaseer op HD of PD behandelingsmodaliteit om óf Floro Proactive, Unilever, Suid-Afrika of Floro ekstra lig margarien te ontvang. Gewig, lengte, liggaamsmassa-indeks (LMI) en middelomtrek (MO) is gemeet, lipogramme en aktiwiteitsvlakke is geëvalueer en dieetinname is bepaal deur die gebruik van die 24-uur herroep metode.

**RESULTATE:** Van die 89 pasiënte wat die ingeligte toestemmingsvorm onderteken het, het 73 die studie voltooi. Die gemiddelde ouderdom was 39 ± 10,5 en 42 ± 12,2 jaar vir PD en HD onderskeidelik en die gemiddelde duur van dialise was 6 jaar vir HD en 4 jaar vir PD. Die meeste van die HD en PD deelnemers het 'n normale LMI en die meeste van die HD pasiënte het 'n normale middelomtrek gehad. Die meerderheid van die deelnemers is as matig aktief geklassifiseer. Die gemiddelde dieetaanbevelings om hartsbeskermende effekte teweeg te bring, soos aanbeveel deur die riglyne was nie voldoende vir die HD en PD groepe onderskeidelik in terme van proteïen (73% (73-78%) en 81% (78-81%) proteïen per ideale liggaamsgewig) en die totale energie (72% (72-88%) en 88% (78-92%) van die totale energie per ideale liggaamsgewig), en die verskillende bronne van vet (113% (112-113%) en 82% (78-82%) versadigde vet, 131% (131-136%) en 117% (104-117%) poli-onversadigde vet, en 43% (43-45%) en 41% (39-41%) van die mono-onversadigde vet) en koolhidrate (90% (90-92%) en 107% (106-107%) vir die persentasie koolhidraat inname met 67% (67-71%) en 58% (58-60%) van die vereiste vesel) nie. Die gemiddelde totale cholesterol, LDL-cholesterol, HDL-cholesterol en trigliseriede vlakke van die deelnemers was by basislyn 4,79 ± 1,39 mmol / l en 3,51 ± 0,79 mmol / l; 3,00 ± 1,07 mmol / l en 1,95 ± 0,64 mmol / l; 0,99 ± 0,33 mmol / l en 1,06 ± 0,05 mmol / l; en 1,74 ± 0,94 mmol / l en 1,07 ± 0,49 mmol / l onderskeidelik vir PD en HD deelnemers. Daar was geen statisties beduidende verband tussen totale cholesterol, LDL-cholesterol, HDL-cholesterol en

trigliseriede vlakke van die deelnemers en die toepaslike gebruik van die onderskeie margariene (toets versus kontrole) nie. Die toetsmargarien het wel 'n nie-beduidende positiewe assosiasie met 'n verlaging in totale cholesterol en LDL cholesterol in ESNV pasiënte wat onderskeidelik HD of PD ontvang gehad. LMI, middelomtrek, aktiwiteitsvlak en 'n dieet wat in ooreenstemming met die riglyne is, het nie 'n beduidende rol in die verandering in totale cholesterol en LDL-cholesterol vlakke van deelnemers gespeel nie .

**BESPREKING:** Die algehele dieetassessering het getoon dat die deelnemers se gewoontelike inname nie geskik is vir hartsbeskermende effekte ten opsigte van vesel en vet nie. Dit kon wel die doeltreffendheid van die steroolverrykte margarien beïnvloed het. ESNV pasiënte kan moontlik voordeel van insluiting van plantsterole in die dieet hê, seine dat die plantsteroolverrykte margarien wel ‘n tendens getoon het om totale en LDL cholesterol vlakke te verlaag, al was dit nie statisties beduidend nie.

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## CONTRIBUTIONS BY PRINCIPAL RESEARCHER AND FELLOW RESEARCHERS

The principal researcher (Nicole Pereira Ribeiro) developed the idea and the protocol for the research project. The principal researcher planned the study, undertook all data collection and captured the data for analysis. The data was analysed with the assistance of a statistician (Prof. DG Nel). The principal researcher interpreted the data and drafted the thesis. The supervisors, Dr. S Potgieter and Prof. S Naicker, provided input at all stages of the project and revised the protocol and thesis. The thesis was language edited by the Language Centre of Stellenbosch University.

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# LIST OF ABBREVIATIONS

| | |
|---|---|
| 4D | The Dutch Diabetic Dialysis Study |
| ABCG5/ABCG8 ATP | Binding cassette transporters G5 and G8 |
| ACAT2 | Acyl CoA-cholesterol acyltransferase-2 |
| ACC / AHA | American College of Cardiology / American Heart Association |
| Apo | Apolipoprotein |
| ASCVD | Atherosclerotic Cardiovascular Disease |
| AURORA | A study to evaluate the use of Rosuvastatin in participants on regular HD: An assessment of survival and cardiovascular events |
| BMI | Body Mass Index |
| CAPD | Continuous Ambulatory Peritoneal Dialysis |
| CE | Cholesterol ester |
| CGA | Cause, GFR Category, and Albuminuria category |
| CHD | Coronary Heart Disease |
| Chol, C | Cholesterol |
| CKD | Chronic Kidney Disease |
| CM-C | Chylomicrons |
| CMJAH | Charlotte Maxeke Johannesburg Academic Hospital |
| CMr-C | Cholesterol-rich remnant |
| CVD | Cardiovascular Disease |
| DHA | Docosahexanoic acid |
| EPA | Eicosapentanoic acid |
| ESC / EAS | European Society of Cardiology and European Atherosclerosis Society |
| ESRD | End Stage Renal Disease |
| FFA | Free Fatty Acids |
| GFR | Glomerular Filtration Rate |
| HD | Hemodialysis |
| HDL | High Density Lipoprotein |
| HPS | Heart Protection Study |
| IDL | Intermediate Density Lipoprotein Initiative |
| IBW | Ideal body weight |
| KDOQI | Kidney Disease Outcome Quality Initiative |
| LDL | Low Density Lipoprotein |

| | |
|---|---|
| LDL-R | Low Density Lipoprotein-receptor |
| Lp | Lipoprotein |
| MTP | Microsomal triglyceride transfer protein |
| MUFA | Monounsaturated fatty acids |
| n-3 | Omega-3 |
| n-6 | Omega-6 |
| NaCl | Sodium Chloride (salt) |
| NCEP ATPIII / IV | National Cholesterol Education Programme Adult Treatment Panel III / IV |
| NHANES | National Health and Nutrition Examination Survey |
| NHLBI | National Heart, Lung, and Blood Institutes' |
| NKF/ KDOQI | National Kidney Foundation-Kidney /Disease Outcome Quality |
| NPC1L1 | Nieman-Pick C1-Like transporter |
| NYHA II-IV | New York Heart Association class II-IV |
| PD | Peritoneal Dialysis |
| PEM | Protein energy malnutrition |
| PUFA | Polyunsaturated fatty acids |
| PVD | Peripheral Vascular Disease |
| RCT | Randomised Control Trial |
| RRT | Renal Replacement Therapy |
| SF | Saturated Fat |
| SFA | Saturated Fatty Acids |
| SHARP | Study of Heart and Renal Protection |
| TE | Total energy |
| TG | Triacylglycerol |
| TLC | Therapeutic Lifestyle Change |
| VLDL | Very Low Density Lipoprotein |
| WC | Waist Circumference |

# CHAPTER 1: MOTIVATION AND BACKGROUND

## 1.1. RESEARCH QUESTION

Would an additional therapeutic cholesterol-lowering strategy, as indicated in the therapeutic lifestyle change (TLC) guidelines, including the addition of phytosterol-enriched spread at a dosage of 25 g/d (2-3 g/day of sterol), reduce low density lipoprotein (LDL) cholesterol levels, and/or augment the LDL cholesterol-lowering effect of other strategies (such as medication and diet) without influencing high density lipoprotein (HDL) or triacylglycerol (TG) levels in ESRD patients receiving HD or PD at CMJAH?

## 1.2. AIM AND OBJECTIVES

The aim of this study is to measure the effectiveness of including plant sterol-enriched margarine in the usual diet of ESRD patients receiving peritoneal dialysis and hemodialysis treatment at CMJAH.

**Objectives:**

- To determine whether the addition of 25 g/d (2-3 g/d plant sterol) plant sterol-enriched margarine to the usual diet of patients with ESRD will reduce LDL cholesterol levels.
- To capture the patient's demographic information, as well as gather information regarding the diagnosis, progression and risk factors for developing kidney failure.
- To determine the patient's nutritional status in terms of body weight and height, body mass index and waist circumference where applicable, in relation to their risk for cardiovascular disease.
- To determine if the patients' receiving renal replacement therapy (RRT) usual intake, assessed using a 24hour recall, is adequate or not, and meets the criteria for being cardioprotective in terms of the Kidney-disease outcome quality initiative (K/DOQI) and TLC guidelines.

## 1.3. HYPOTHESIS

The inclusion of plant sterols in the standard renal diet as specified by K/DOQI will reduce the lipid profiles in ESRD patients receiving chronic RRT at CMJAH.

## 1.4. MOTIVATION FOR STUDY

Cardiovascular disease is the leading cause of morbidity and mortality in dialysis patients. Dyslipidemia occurs particularly frequently in ESRD patients, but the benefit of lipid lowering treatment still needs to be proven in this group. A multidisciplinary, collaborative approach is essential to help patients improve their cholesterol, LDL, HDL and TG levels to reduce cardiovascular risk. This can be accomplished by adherence to lifestyle and pharmacological regimens which are generally extrapolated from the general population to

have a similar effect in patients with ESRD. There is an urgent need to confirm guideline statements from studies in the general population in patients with ESRD. There are reasonable doubts as to whether RCTs from the general population regarding the use of plant sterols and stanols can be extrapolated to all patients with ESRD, as most trials in the general population have excluded patients with elevated serum creatinine and Stage V ESRD.

# CHAPTER 2: LITERATURE OVERVIEW

## 2.1. INTRODUCTION

Mortality secondary to cardiovascular disease (CVD) in patients with end stage renal disease (ESRD) is 10 to 30 times higher than in their population counterparts not suffering from ESRD.[1] Atherosclerotic CVD is a major medical and public health concern in Western and developing countries all over the world, and it is the most common cause of death among patients maintained on long term dialysis.[2] This may be because ESRD promotes or enhances the development of risk factors and/or because ESRD and CVD may in many cases share the same risk factors.[3] Traditional risk factors for ESRD related to this increased prevalence include: older age, gender (males), presence of comorbid conditions (diabetes mellitus, hypertension and left ventricular hypertrophy/systolic dysfunction), smoking, dyslipidemia, physical inactivity, family history of CVD, and menopause. Evidence from observational studies also suggest that in addition to these traditional risk factors, non-traditional risk factors for the pathogenesis of CVD include that of chronic volume overload, abnormal calcium and phosphate metabolism, vitamin D deficiency, anaemia and thrombogenic factors, systemic inflammation, increased homocysteine levels, malnutrition, albuminuria, altered nitric oxide or endothelin balance, oxidative stress and other aspects of uraemia in patients with ESRD. However, unlike dyslipidemia, there are no intervention trials from patients in the general population or in those with ESRD demonstrating that the modification of these non-traditional risk factors reduces the risk of developing CVD. The traditional and non-traditional risk factors, dyslipidemia in particular, are likely to place ESRD patients into the highest cardiovascular risk group.[1,4,5] The American College of Cardiology (ACC) has categorised these risk factors into four categories that match the intensity of risk factor management with the evidence for an association with CVD, clinical usefulness, and response to therapy, depicted in Table 1.[2] The evidence-based approach used is similar to that endorsed by the Agency for Health-Care Research and Quality. Level I (+++) evidence indicates that there is strong evidence that the practice improves net health outcomes, and benefits substantially outweigh harm. Level II (++) evidence indicates that there is moderate evidence that the practice improves net health outcomes; and level III (+) evidence indicates that the recommendation is based on either weak or poor evidence, or on the opinions of reviewers that the practice might improve net health outcomes.[5] A multifactorial risk reduction (MFRR) on both disease severity and clinical outcomes of these patients improves endothelial function, decreases prothrombotic mechanisms, and can stabilise and regress plaque and prevent plaque rupture, thus reducing the risk of acute myocardial infarction and stroke.[6]

**Table 1:** The American College of Cardiology categorisation of risk factors with associated [a]CVD

| | Risk Factor | with CVD Epidemiologic | with CVD Clinical Trials | Usefulness | Nonpharmacological Therapy | Pharmacological Therapy |
|---|---|---|---|---|---|---|
| Category I* | Smoking | +++ | ++ | +++ | +++ | ++ |
| | LDL Cholesterol | +++ | +++ | +++ | ++ | +++ |
| | High Fat/Cholesterol Diet | +++ | ++ | ++ | ++ | - |
| | Hypertension | +++ | +++ | +++ | + | +++ |
| | Left Ventricular Hypertrophy | +++ | + | ++ | - | ++ |
| | Thrombogenic factors | +++ | +++ | + | + | +++ |
| Category II** | Diabetes Mellitus | +++ | + | +++ | ++ | +++ |
| | Physical Inactivity | +++ | ++ | ++ | ++ | - |
| | HDL Cholesterol | +++ | + | +++ | ++ | + |
| | Triglycerides, LDL Cholesterol | ++ | ++ | +++ | ++ | +++ |
| | Obesity | +++ | - | +++ | ++ | + |
| | Postmenapausal status (women) | +++ | - | +++ | - | +++ |
| Category III*** | Psychosocial factors | ++ | + | +++ | + | - |
| | Lipoprotein (a) | + | - | + | - | + |
| | Homocysteine | ++ | - | + | ++ | ++ |
| | Oxidative stress | + | - | - | + | ++ |
| | No alcohol consumption | +++ | - | ++ | ++ | - |
| Category IV**** | Age | +++ | - | +++ | - | - |
| | Male gender | +++ | - | +++ | - | - |
| | Low socioeconomic status | +++ | - | +++ | - | - |
| | Family history of early onset CVD | +++ | - | +++ | - | - |

*Risk factors for which interventions have been proven to lower CVD risk; **risk factors for which interventions are likely to lower CVD risk; ***risk factors associated with increased CVD risk that, if modified, might lower risk; ****risk factors associated with increased CVD risk that cannot be modified)

+' week, somewhat consistent evidence; '++' moderately strong, rather consistent evidence; '+++' Very strong, consistent evidence; '-' No/ poor evidence

*Krummel DA. Medical Nutrition Therapy in Cardiovascular disease. Ch. 35. Pg 860-899. IN: Krause Food & Nutrition Therapy. Ed. Mahan LK & Escott-Stump S. WB Saunders Company, London.2000*[2]

*[a]CVD Cardiovascular disease; [b]LDL Low density lipoprotein, [c]HDL High density lipoprotein*

End stage renal disease is characterized by many features of the metabolic syndrome (insulin resistance, obesity, hypertension, and dyslipidemia) which are CVD risk factor as they comprise of established CVD risk factors.[4,7] Atherogenic dyslipidemia associated with the metabolic syndrome, which includes high triacylglycerol (TG), low high density lipoprotein (HDL), and increased LDL cholesterol with the latter mostly in PD patients only; considered the triad of lipid abnormality (Table 2) is common in ESRD patients receiving renal replacement therapy (RRT).[1,6,8,7] These patients may have normal or elevated levels of plasma lipids depending on their treatment regime (Table 3).

Abnormalities in lipid metabolism are detectable from early stages (stages 3-5 Chronic kidney disease (CKD)) of renal failure, and may be secondary to increased hepatic production of lipoproteins as well as a reduced metabolic clearance of LDL cholesterol and as a result their lipid profile is highly atherogenic.[9] Several large scale five year trials (4D, AURORA, SHARP) including CKD patients have stated statins (either mono or dual therapy) to be considered safe and able to reduce Coronary heart disease (CHD) mortality and morbidity by approximately 30%. Assessment of these studies lead to the investigation of the individual response to dietary cholesterol intake and the current treatment modalities used to try reduce cholesterol levels and classify them as either 'hypo-' or 'hyper-responders' (decreased basal rates of cholesterol synthesis and increased serum cholesterol levels secondary to exaggerated response to dietary cholesterol intake respectively). Rogacev et al concluded that ESRD patients receiving HD to be the latter, possibly

owing to reduced hepatic clearance of chylomicrons and VLDL or due to decreased endogenous cholesterol synthesis secondary to enhanced cholesterol absorption so as to maintain homeostasis. Hence future clinical decision-making regarding treatment in this subgroup of patients depending on their mechanism of action was identified as something that will need to be reviewed in the future.[10,11,12]

**Table 2:** Dyslipidemia as defined in the Adult Treatment Panel III Guidelines[2]

| **[a]LDL cholesterol (mmol/L)** | |
|---|---|
| <2.59 | Optimal |
| 2.59 – 3.34 | Near/ Above Optimal |
| 3.36 – 4.11 | Borderline High |
| 4.14 – 4.89 | High |
| ≥4.91 | Very High |
| **Total cholesterol (mmol/L)** | |
| <5.17 | Desirable |
| 5.17 – 6.18 | Borderline High |
| ≥6.21 | High |
| **[b]HDL cholesterol (mmol/L)** | |
| <1.03 | Low |
| ≥1.55 | High |

[a]LDL Low Density Lipoprotein; [b]HDL High Density Lipoprotein

A decreasing glomerular filtration rate (GFR) is associated with CVD independently of other risk factors; in a recent survey in Europe the standardised cardiovascular mortality rate was 30 per 1000 person years (95% CI 37.2 – 39.0) higher in patients starting dialysis than in the general public. Thus ESRD is itself seen as a secondary cause of CVD dyslipidemia.[9,13] In this subgroup of patients, despite adjusting for all possible confounding variables increased cholesterol levels were an independent predictor of mortality.[9] Management of dyslipidemia should be undertaken in conjunction with other modifiable traditional risk factors for CVD in this subgroup of patients to reduce the overall risk of atherogenic CVD. As a result, it is the primary target of cholesterol-lowering therapy as stated by the National Cholesterol Education Programme (NCEP) Adult Treatment Panel III (ATPIII), the American College of Cardiology and the American Heart Association (ACC/AHA), and the European Society of Cardiology and European Atherosclerosis Society (ESC/EAS).[6,9,14,15,16,17] These recommendations based on randomised control trials (RCTs), systematic reviews, and meta analyses of RCT are intended to provide a strong evidence-based foundation for the treatment of cholesterol for the primary and secondary prevention of ASCVD; the recommendations are designed to inform clinical judgement, not to replace it.[18] The ACC/AHA expert panel updated their guidelines in 2013 to assist in managing lipid disorders and incorporate refinements in risk stratification

based on critical review of emerging data. Previously the panel advocated the treat-to-cholesterol target paradigm and that lowest is best (these strategies have been widely used for the past 15 years). Problems with this are that current clinical trial data do not indicate what the target should be, there is uncertainty about the magnitude of additional ASCVD risk reduction that would be achieved with one target lower than the other, and the trial does not take into account potential adverse effects from multidrug therapy that might be needed to achieve a specific goal. New recommendations suggest that the appropriate intensity of statin therapy should be used to reduce ASCVD risk in those most likely to benefit.

**Table 3:** Lipid abnormalities in [a]ESRD [1]

| **Factor** | **[b]PD** | **[c]HD** |
|---|---|---|
| Total cholesterol | ↑ | Normal |
| [d]LDL cholesterol | ↑ | Normal |
| [e]HDL cholesterol | ↓ | ↓ |
| Triglycerides | ↑↑ | ↑ |
| [f]ApoB protein | ↑↑ | Normal |
| [g]Lp(a) | ↑↑ | ↑↑ |
| LDL oxidation | ↑ | ↑ |

*[a]ESRD End stage renal disease; [b]PD: Peritoneal dialysis; [c]HD: Hemodialysis; [d]LDL Low density lipoprotein; [e]HDL High density lipoprotein; [f]ApoB: Apolipoprotein B; [g]Lp(a): Lipoprotein (a)*

Cholesterol-lowering agents, like statins, are recommended for individuals at increased ASCVD risk who are most likely to experience a net benefit in terms of the potential for ASCVD risk reduction and the potential for adverse effects, but the primary treatment thereof should be lifestyle modification (i.e. adhering to a heart healthy diet, regular exercise habits, avoidance of tobacco products, and maintenance of healthy weight), a crucial component of health promotion and ASCVD risk reduction, both prior to and in conjunction with the use of cholesterol-lowering agents. Overall it is important to keep in mind that percent reduction is used to assess response to therapy and adherence, and should not be used as a performance standard. Biological variability in the response to therapy aimed at improving lipid profiles is thus seen in such instances when looking at percent reduction (some individuals may have less than an

average response to certain treatments). The initial cholesterol value is the primary predictor of cholesterol response because the higher the initial cholesterol, the greater the cholesterol-lowering lifestyle and pharmacological effect.[18,19] The nutritional factors that affect LDL levels may be seen in Table 4.[6]

**Table 4:** Nutrition factors that affect [a]LDL cholesterol[6]

| |
|---|
| **Increased LDL cholesterol** |
| Saturated fat (SF) and trans fatty acids |
| Dietary cholesterol |
| Excess body weight |
| **Decreased LDL cholesterol** |
| Polyunsaturated fatty acids (PUFA) |
| Soluble Fibre |
| Plant stanols/ sterols |
| Weight Loss |
| Isoflavone-containing soy protein (limited evidence) |
| Soy protein |

[a]*LDL Low density lipoprotein*

Numerous studies have reported the atherogenic potential of saturated fats, trans fatty acids, and cholesterol, and the beneficial effects of fibre, plant sterols, omega-3 fatty acids, a Mediterranean diet, and other plant-based approaches.[19] Appropriate dietary manipulations (first line therapy) are able to correct dyslipidemia together with pharmacological therapy (second line therapy), if necessary.[9] First line therapy has been shown to moderately control increased TG and LDL cholesterol (Table 1). In the INTERHEART cross-sectional study in 52 countries which ranked nine cardiovascular risk factors, dyslipidemia alone accounted for most of the population attributable risk factor for myocardial infarction. Reductions in LDL cholesterol levels achieved by treatment with diet, statins, or bile acid sequestrants have been demonstrated in meta-regression analyses to reduce cardiovascular morbidity and mortality significantly. Lifestyle, encompassing dietary habits, must be considered particularly as extensive nutritional and behavioural changes may lower LDL cholesterol by up to 20%.[20]

The National Kidney Foundation (NKF)- K/DOQI and Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend that dyslipidemia should be evaluated at onset of chronic renal failure (CRF), and patients with increased fasting cholesterol, LDL cholesterol and/ or TG levels should be advised to follow the TLC dietary guidelines for its cardioprotective effects.[5,15,16,17,19,21] It has been said that the prevalence of deaths associated with CVD is decreased by as much as 70% with improvements in the management and treatment of modifiable risk factors by modifying dietary choices and lifestyle as indicated in the TLC

guidelines.[5,15,16,17,19,21,22,23,24] The TLC diet emphasises reduction in saturated fat and trans fatty acids (<7% combined), and cholesterol (<200 mg/day), promotes the inclusion of viscous fibre (10-25 g/day) and considers the inclusion of plant sterols and stanols (2 g/day; phytosterols found in plant foods, they are structurally similar to cholesterol, but are not synthesised by the human body) in the diet.[2,4,5,19,22] Plant sterols and stanols in particular are useful therapeutic cholesterol-lowering agents since daily intake of 2-3 g lowers LDL cholesterol concentrations by 10-15% as reported in various populations (excluding ESRD patients).[25] They can be included in the diet in the form of an enriched spread, as part of their typical dietary intake. The effects thereof are increased when combined with a cholesterol-lowering diet (as indicated in the TLC guidelines) and the use of cholesterol-lowering drugs. The primary aim of the TLC diet is to reach LDL goal, intensify weight management, and increase physical activity (modifiable risk factors).[2,19,22]

While the efficacy of plant sterols and stanols has been demonstrated to reduce LDL cholesterol levels in the general population, it is lacking in the ESRD population. As mentioned previously, in respect of the study done by Rogacev KS et al, ESRD patients receiving HD have been identified as 'Hyper-responders' which gives insight into how differing results of cholesterol-lowering trials may affect future clinical decision-making processes regarding the treatment thereof.[10,11,12] Therefore the aim of this study is to assess whether ESRD patients receiving RRT at CMJAH are more likely to undergo an improvement in their lipid profile during eight weeks where plant sterols are included as part of their diet. If so, the possible cost saving thereof could be of benefit, especially in countries experiencing financial constraints. Current literature identified the need for more studies to clarify the specific effects of dietary components such as sterols on the health of ESRD patients. A conceptual framework for the multifactorial reduction on disease severity and clinical outcomes for ESRD patients receiving RRT can be seen in Figure 1 below.

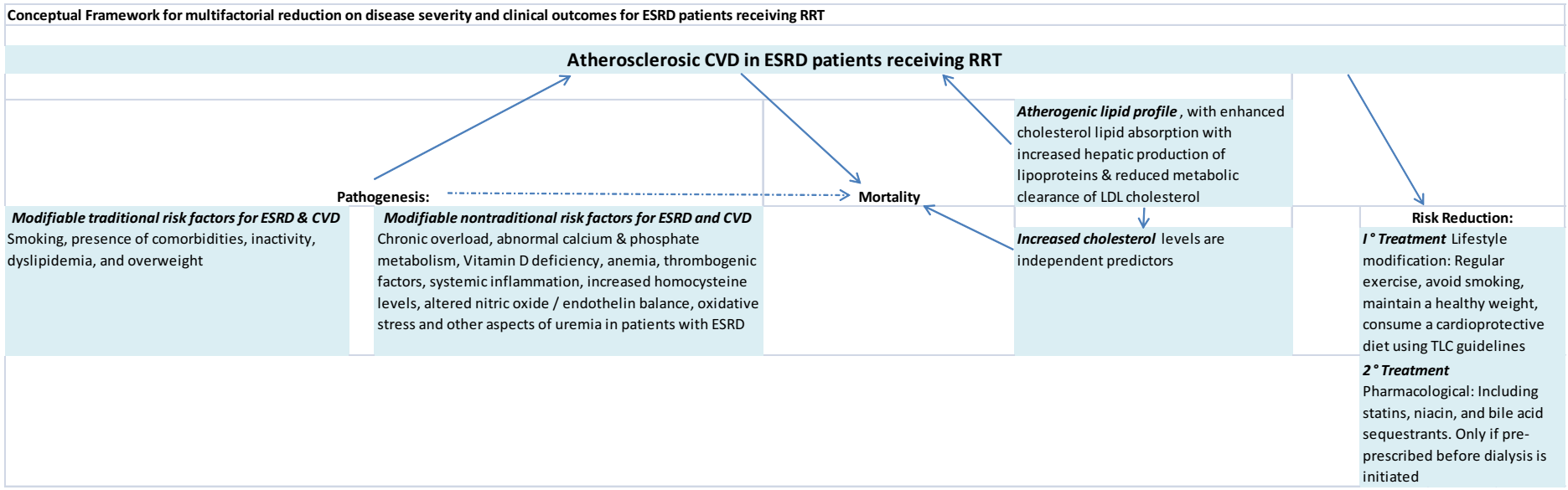



**Figure 1:** Conceptual framework for multifactorial reduction on disease severity and clinical outcomes for ESRD patients receiving RRT

## 2.2. PATHOPHYSIOLOGY AND ETIOLOGY OF CVD IN RENAL DIALYSIS PATIENTS

End stage renal disease (ESRD) is a multifactorial disease that involves a complex interaction of risk factors, genetics, diet and lifestyle, all of which interact to cause CKD.[22] According to Kidney Disease Improving Global Outcomes (KDIGO) 2013 clinical practice guideline for the evaluation and management of CKD, CKD is now classified on the basis of cause, glomerular filtration rate category (GFR, an estimate from serum creatinine using an established formula), and albuminuria category (CGA) rather than GFR in isolation as previously done. By including cause of CKD, GFR category, CGA (earliest marker of glomerular diseases, which generally appears before the reduction in GFR and is associated with abnormalities in coagulation, duration and severity of disease itself and hypertension that is strongly associated with progression of CKD; and an adverse lipid profile with increased total cholesterol, triglycerides and lipoprotein(a) and decreased high density lipoprotein levels), other risk factors and comorbid conditions (hypertension, obesity, vascular disease, diabetes); the outcome of CKD can be better predicted as seen in Table 5.[4,5,22] Albuminuria and reduced GFR levels were synergistic cardiovascular mortality risk factors in the HUNTS 2 study. The inclusion of CGA staging can be used to inform the need for therapeutic interventions amongst other factors. As a result, progression of CKD is defined as either a progressive decrease in GFR or a progressive increase in albuminuria. The growing interest in understanding and improving the outcomes of patients with kidney disease led to the update of the original 2002; KDOQI guideline whereby those diagnosed with stage III CKD, risk for CVD is increased by 43%, and in those with stage V (category G5) the risk increases by 343%. Those with stage G3a and G3b have more events, which is said to be related to a higher prevalence in these categories. Events occur at a younger age in patients with CKD, suggesting that CKD promotes CVD at an accelerated rate.[6]

**Table 5:** Prognosis of [a]CKD by [b]GFR and albuminuria category[5]

**Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012**

| GFR categories (ml/min/ 1.73m²) Description and range | | | | Persistent albuminuria categories Description and range | | |
|---|---|---|---|---|---|---|
| | | | | A1 | A2 | A3 |
| | | | | Normal to mildly increased | Moderately increased | Severely increased |
| | | | | <30 mg/g <3 mg/mmol | 30-300 mg/g 3-30 mg/mmol | >300 mg/g >30 mg/mmol |
| | G1 | Normal or high | ≥90 | | | |
| | G2 | Mildly decreased | 60-89 | | | |
| | G3a | Mildly to moderately decreased | 45-59 | | | |
| | G3b | Moderately to severely decreased | 30-44 | | | |
| | G4 | Severely decreased | 15-29 | | | |
| | G5 | Kidney failure | <15 | | | |

*[a]CKD Chronic Kidney Disease; [b]GFR Glomerular Filtration Rate; [c]KDIGO Kidney Disease Improving Global Outcomes; Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red: very high risk*

By definition ESRD is the abnormality of the structure or function of both kidneys, lasting greater than 3 months, and often progressive and irreversible. Contributing causes of CKD include diabetic nephropathy, hypertension, infection (chronic pyelonephritis or sepsis secondary to severe urinary tract infection), polycystic kidney disease, tumour (multiple myeloma, amyloidosis), and can be familial (Alport's syndrome). When CKD progresses so that the patient's kidneys no longer function sufficiently to maintain life therefore necessitating dialysis or transplant (stage V), ESRD results. [5,15,16,17,21,23,24]

Dialysis is a means of artificial filtration of blood when kidney failure has progressed to stage V. The two main types are hemodialysis (HD) and peritoneal dialysis (PD). In HD, blood from a vascular access site (fistula, graft or permcatheter) circulates through a dialysis filter (waste products removed by diffusion and fluids by ultrafiltration), where it is filtered and returned to the parallel vein. In PD, the patient's own peritoneum serves as the filtration membrane.[2,9,23,24,26] The dialysate, a solution of dextrose and electrolytes of variable osmolality, enters via a catheter penetrating the abdominal wall into the peritoneal cavity. Continuous ambulatory peritoneal dialysis (CAPD) is a type of peritoneal dialysis used at CMJAH. This involves the patient manually exchanging the dialysate four to five times per day, over a 24-hour treatment period.[9,23,24] The daily amount of dextrose (600-800kcal/day) absorbed depends on the concentration of

dextrose used for each exchange, and the number of exchanges (Table 6). The dextrose concentration can be altered either to increase or decrease the amount of fluid removed. Currently three concentrations are available (Table 6). The more concentrated the dialysate the more fluid is removed and dextrose kilocalories absorbed. Dietary intake must be modified to account for the energy absorbed from the dialysate.[23,24]

**Table 6:** Concentration of dextrose absorbed with CAPD[25]

| Dialysate dextrose concentration | Grams of dextrose/L | kcal/L from dextrose | kcal/L with [a]CAPD (60%)* |
|---|---|---|---|
| 1.50% | 15g | 51kcal | 31kcal |
| 2.50% | 25g | 85kcal | 51kcal |
| 4.25% | 42.5g | 144.5kcal | 86.7kcal |

**60% dextrose absorbed with [a]CAPD Continuous Ambulatory Peritoneal Dialysis*

***each gram of dextrose = 3.4kcal*

*E.g. Energy/L x Total Volume*

Cardiovascular disease (CVD, umbrella term) includes all diseases of the heart and blood vessels, such as hypertension, CHD, stroke, rheumatic heart disease and congestive heart failure.[2,23,24,26] The pathogenesis of atherosclerosis involves fatty plaques or atheromas (lipids, primarily oxidised cholesterol) developing in the intimal layer of the arterial wall. The causes of endothelial dysfunction appear to be diverse and attributable to smoking (decreases HDL, and increases VLDL), diabetes (poor glucose control measured with glycosylated haemoglobin levels), hypertension (140/90mmHg, or use of antihypertensive medication [AHA, 2001], results in vascular injury and stresses to the myocardium), oxidative damage (oxidised LDL), the aging process, hyperhomocysteine, hypercholesterolemia, unhealthy diet (high in saturated fat and cholesterol), lack of a healthy lifestyle, lack of activity, and overweight.[2,23,24,25,26] The risk of CVD is much higher with multiple risk factors. Computer modelling studies have shown that 25% of the decline in CHD is attributable to primary prevention and 70% to behavioural changes affecting risk factors or improvements in treatment. Thus better treatment and prevention efforts, such as lifestyle changes to modify risk factors relate to this decrease in mortality (Hunink et al, 1997).[2,26] Reduced GFR by itself is associated with hyperlipidaemia (increased cholesterol and TG) placing them in the highest risk category for CVD.[15,16,17,21,27]

Coronary heart disease by definition is the narrowing of the lumen of arteries supplying blood to the heart muscle as a result of atheromatous plaque on the arterial walls.[15,16,17,21] The lesions that develop are the result of the proliferation of smooth muscle cells (macrophages) and lymphocytes; formation of macrophages into a connective tissue matrix; and accumulation of lipid and cholesterol in the matrix

around the cells resulting in endothelial dysfunction. Thus, it is an inflammatory and proliferative response to arterial wall injuries.[2,26] Atherosclerosis involves progressive narrowing of the arteries starting from childhood, and limits the blood supply to the cerebral arteries causing strokes; coronary arteries causing pain (angina) and breathlessness on exertion; and intermittent claudication and gangrene in the peripheral circulation.[2,15,16,17,21,22,26] Damaged plaque leads to a clotting response, which may result in a thrombus (rupture of the fibrous plaque cap) detaching from the artery wall and occluding the lumen with subsequent reduced blood flow to the heart (myocardial infarction or heart attack). Kidneys can also be affected by atherosclerosis.[2,15,16,17,21,23,24,26,28,29]

Atherosclerotic CVD (ASCVD) is a major cause of mortality and morbidity in patients with ESRD, secondary to both underlying disease (diabetes mellitus, hypertension, nephrotic syndrome) and a lipid abnormality common among patients with ESRD.[2,26,27] The risk of ASCVD varies depending on the cause of renal disease, the degree of reduction in GFR, the type of lipid abnormalities, and the target population (Table 2).[27] CVD accounts for 41 - 50% of mortality after RRT has commenced and is also prevalent in patients in the early stages of renal disease (Figure 2).[15,16,17,21,23,24] Most ESRD patients have an increased 10-year risk for CHD events, placing them in the highest risk category according to the National Cholesterol Education Programme Adult Treatment Panel III guidelines (NCEP ATP III).[30] The NKF-K/DOQI estimates over 60% of dialysis patients to have lipid abnormalities, and various studies have confirmed the prevalence in this subgroup of patients to be much higher than in the general population.[2,5,26]

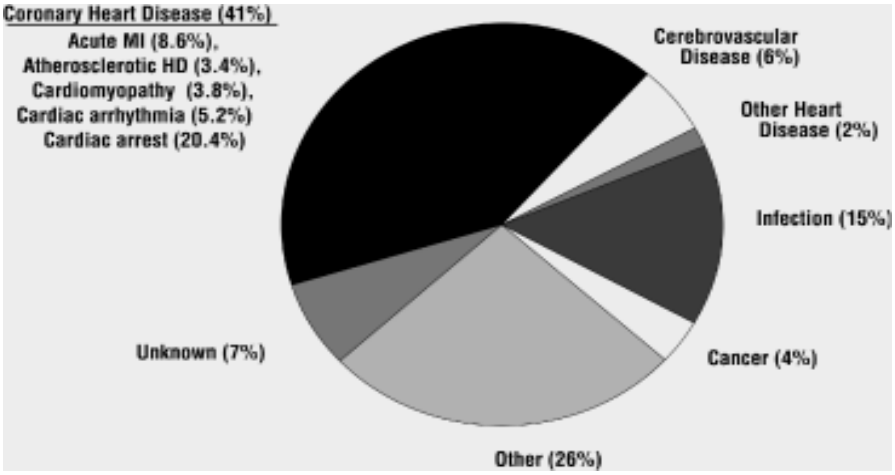



**Figure 2:** Causes of death among patients treated with HD, PD, or kidney transplantation between 1997-99, data from the USRDS 2001 Annual Data Report[4]

Modifiable risk factors in ESRD include: bone disease, anaemia, oxidative stress, infections, obesity, proteinuria, hypertension, hyperglycaemia, smoking, inactivity and dyslipidemia which all coexist in CVD.[31] The last three factors decrease blood flow and potentially increase ESRD damage. Both abnormal

calcium/phosphate metabolism and vitamin D influences the regulation of inflammation, myocardial cell hypertrophy and proliferation, and the regulation of the renin-angiotensin system; thus deficiency thereof is implicated in CVD. Maintenance of haemoglobin levels above 11g/dL is currently recommended to prevent further progression of left ventricular hypertrophy. Oxidant stress is increased in dialysis patients as a result of increased inflammation; malnutrition, uremic toxins, and potentially the dialysis procedure itself thus further increasing CVD risk. Increased serum levels of inflammatory markers (acute phase proteins and cytokines) alter lipoprotein and endothelial structure and function to favour atherogenesis; it also increases atherogenic proteins in serum such as fibrinogen and lipoprotein.[22] The left ventricle increases in size in response to increased blood pressure and increased workload secondary to obesity.[2,26,32] Smoking reduces renal function together with increasing heart failure and peripheral vascular disease. Physical activity of 30 minutes, on most days of the week, of moderate intensity (e.g. climbing stairs, gardening, walking etc.) decreases CHD risk by retarding atherogenesis; increasing the vascularity of the myocardium; increasing fibrinolysis; and modifying other risk factors such as increasing HDL cholesterol, improving glucose tolerance and insulin sensitivity, aiding in weight management, and reducing blood pressure.[2,26] Diabetes (hyperglycaemia) and ESRD are considered CVD risk factors which may in part be attributable to the concurrent presence of other risk factors, such as dyslipidemia, hypertension, and obesity as mentioned previously. The treatment of dyslipidemia, in particular LDL cholesterol, and blood glucose, among the other modifiable risk factors mentioned previously is necessary in this subgroup of patients.[2,26] A meta-analysis of small studies to assess the effect of lipid reduction on the progression of renal disease has shown that lipid reduction may preserve GFR and reduce proteinuria (considered a sign of target organ damage and thus associated with high cardiovascular risk) while correcting dyslipidemia.[5,27]

Thus in addition to hyperlipidaemia, patients exhibit many other risk factors associated with CVD, many of which can be improved with a combination of changes in diet, lifestyle, and physical activity and therefore a multifactorial approach is important.[15,16,17,19,20,21,22]

### 2.3. SERUM LIPIDS AND LIPOPROTEIN TRANSPORT IN RELATION TO CVD AND ESRD

Ninety-eight percent of lipids (cholesterol, TGs, and phospholipids) are carried in the blood as lipoproteins (carrier proteins) which vary in composition, size and density (those with more protein are considered denser).[2,15,16,17,21,26] The physiological role of lipoproteins includes transporting lipid to cells for energy or storage and serving as a substrate for synthesis of prostaglandins, thromboxanes, and leukotrienes. Due to the different metabolic roles, the lipoproteins also vary in atherogenecity.

The carriers of lipids and their lipoproteins are consequently seen as predictors of risk for CVD.[2,26] LDL-cholesterol is the primary target of therapy for dyslipidemia, but attention should also be given to elevated

TG and low HDL-cholesterol levels. ESRD patients are known to have impaired lipoprotein metabolism thus placing them at additional increased risk for CVD as mentioned previously (Table 3). The ATP IV recommends a complete fasting (8-12 hours) lipoprotein profile for screening.[14,15,16,17,20,22]

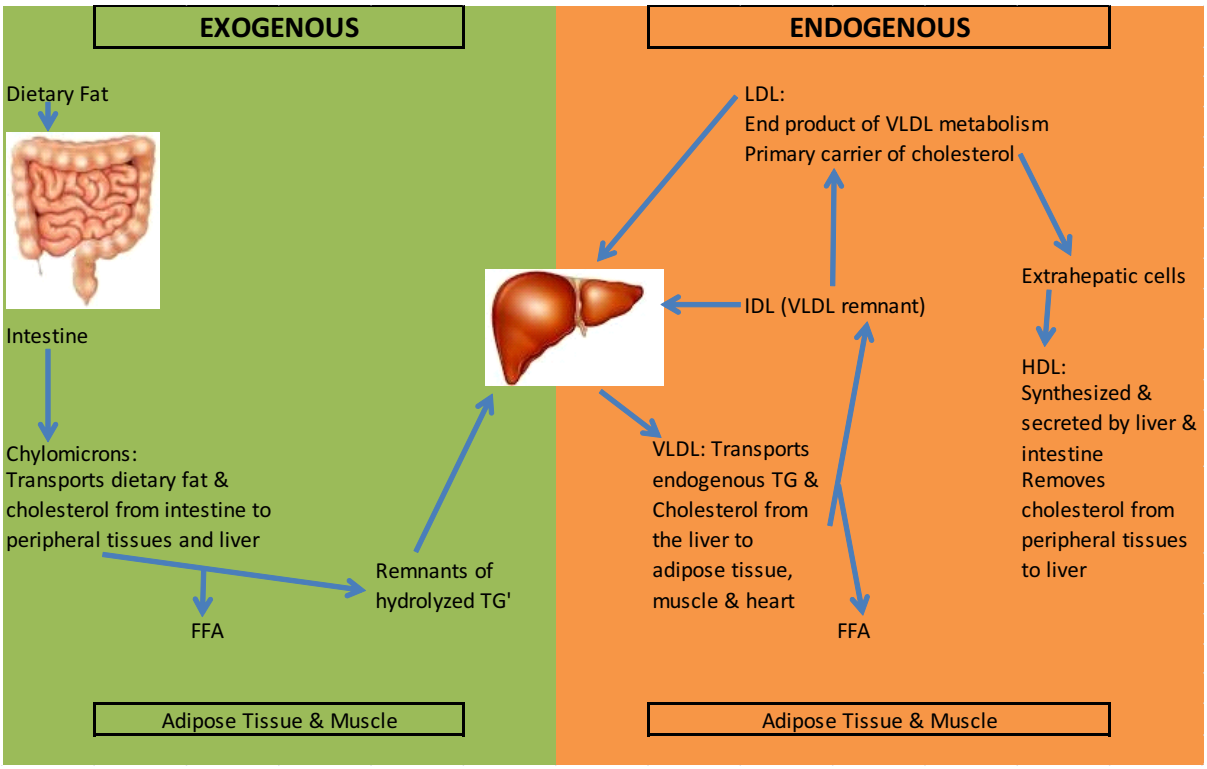
There are five classes of lipoproteins, namely chylomicrons, very low density lipoprotein (VLDL), LDL, HDL and lipoprotein a (Lp(a), which is a complex of LDL with apolipoprotein(a), it is elevated in dialysis patients as part of the inflammatory response, and it is unaffected by diet, exercise and most lipid-lowering medications).[14,15,16,17,20,21]

### 2.3.1. Chylomicrons

Chylomicrons mainly consist of TGs which transport dietary fat and cholesterol from the small intestine into the circulation to peripheral tissues and the liver (Figure 3).[15,16,17,20,21] Approximately 90% of the TGs are hydrolysed and the remnant is released back into the bloodstream where it is metabolized by the liver. It can also deliver cholesterol to the arterial wall and as a result are considered atherogenic (Figure 4). Consumption of high fat meals produces more chylomicrons and resultant remnants. Usually chylomicrons are absent in fasting plasma studies.[2,20,26]

### 2.3.2. VLDL

Very low density lipoprotein is synthesised in the liver, and is a precursor for LDL. Very low density lipoprotein transports endogenous TGs and cholesterol from the liver to adipose tissue, muscles and heart (Figure 3). Very low density lipoprotein is believed at most to be nonatherogenic. VLDL remnants become intermediate density lipoprotein (IDL) and are taken up by the liver or converted to LDL which may become atherogenic when oxidised (Figure 4). A total TG level is a measurement of the TG in VLDL, remnants, and IDL.[2,15,16,17,20,21,26]



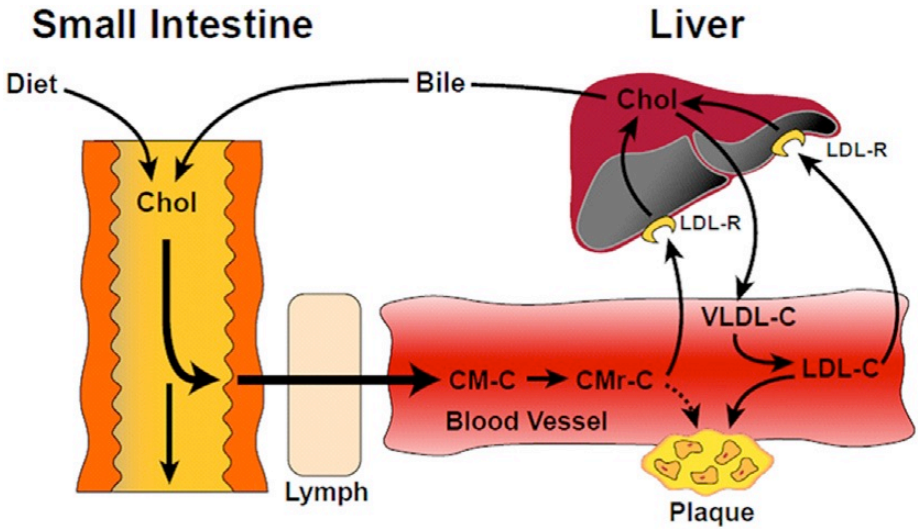

*Silverthorn DU. Human physiology: an integrated approach. 2nd ed. New Jersey:Prentice Hall; 2001*

**Figure 3:** Lipid Metabolism in the body

### 2.3.3. LDL

Low density lipoprotein is the end product of VLDL metabolism. It carries approximately 70% of cholesterol (primary carrier) in the blood supplying the peripheral tissues and liver.[2,15,16,17,20,21,26] Excess LDL enters the blood vessel walls and builds up under the lining forming plaques which may result in inflammation and bleeding into the area followed by calcification and obstruction of the blood flow (Figure 4). Because LDL is correlated with atherogenic remnant proteins it is considered a risk factor for atherogenesis and is conclusively linked to CHD development and acute events (Figure 4).[23,24] Data from drug trials indicate that a reduction in LDL cholesterol levels of about 10% could be expected to reduce the incidence of ischemic heart disease by about 12-20% over five years.[32] LDL levels above 2.6 mmol/L (Table 3) are associated with this increased risk. Numerous studies by Degoulet, Lowrie, Liu etc have found that low serum total cholesterol levels (<2 mmol/l) are associated with increased mortality (high CV death) in dialysis patients even after controlling for other biochemical factors (not seen in the general public) possibly linked to 'malnutrition inflammation complex syndrome' – malnutrition, inflammation, atherosclerosis, MIA (characterized by undernutrition, hypoalbuminemia, increased inflammation, and consequent atherosclerosis) with increased risk of mortality from stroke, cancer and other noncardiovascular diseases, as it is seen as an indicator of insufficient protein and energy intake (malnutrition). The atherogenic effect of LDL cholesterol is apparent in the genetic disease familial hypercholesterolemia, which is characterized

by few or no LDL receptors, resulting in defective LDL metabolism, elevated levels in plasma, and severe premature atherosclerosis and CHD. The number and activity of LDL receptors in the liver, adrenal and other tissues are major determinants of LDL cholesterol levels in the blood (Figure 4).[2,20,26,33]




*Cholesterol (Chol, C) entering the intestinal lumen primarily from the bile and diet is absorbed to varying degrees and packaged in chylomicrons (CM-C) for transport via the lymph into the circulation. Therein, hydrolysis of much of the triacylglycerol present in the nascent CM results in the formation of cholesterol-rich remnant particles (CMr-C) that are ordinarily rapidly cleared from the circulation by the liver. Delivery of excess intestinal cholesterol to the liver can result in suppression of LDL-receptor (LDL-R) activity and endogenous cholesterol synthesis, or acceleration of hepatic VLDL cholesterol (VLDL-C) secretion, or both. Such events will potentially raise plasma LDL cholesterol (LDL-C) concentration. If hepatic clearance of CMr is delayed, then these particles may contribute directly to plaque formation. Together, these various pathways illustrate how agents that limit cholesterol absorption may elicit favourable changes in atherogenic plasma lipoproteins that culminate in attenuating plaque formation.*[20]

**Figure 4:** Scheme illustrating the potential impact of cholesterol absorption from the small intestine on plasma levels of chylomicron remnants and LDL cholesterol, with detrimental effects on the vascular wall.

Researchers believe that oxidised LDL and lipid oxidation products (when convert macrophages into foam cells) are involved in all stages of CHD.[15,16,17,23,24] Oxidation of LDL in the vessel wall speeds up the atherogenic process by stimulating auto antibodies, increasing LDL uptake, and increasing vascular tone and coagulability.[2,26] Lowering LDL cholesterol levels delays progression of atherogenesis, regresses' lesions, and reduces morbidity and mortality associated with CHD. Data from the Heart Protection Study (HPS, the first large RCT of statin therapy) which included 6748 patients with PVD demonstrated that aggressive LDL lowering was associated with a marked reduction in cardiovascular events (myocardial infarctions, stroke, revascularisations, and vascular disease).[6]

Total cholesterol and LDL cholesterol levels are highly correlated. Both are thus primary targets for intervention efforts (Figure 4).[2,26] Total or LDL cholesterol is highest in patients with ESRD.[27] Patients with

increased LDL together with low HDL and high levels of TG are considered to be more at risk for CHD than elevated LDL levels alone. A decrease of 0.03mmol/L in LDL cholesterol results in about 1-2% decrease in relative risk for CHD.[2,26]

Factors that increase LDL levels include aging (≥ 45years for men and ≥55 years for women), genetics (premature history of CVD in first degree male relative <55 years and <65 years if female), diet (high in saturated fat and cholesterol), cigarette smoking, reduced HDL cholesterol, diabetes, hypothyroidism, nephrotic syndrome, obstructive liver disease, obesity (increased production of apo B-containing lipoproteins: VLDL and consequently LDL) and some steroid and antihypertensive drugs. Dietary adaptation includes substituting saturated fat (SF) and trans fatty acids for monounsaturated (MUFA) and polyunsaturated fat (PUFA; less likely to be oxidised), and including soluble fibre, soy protein, stanols and sterols, and overall weight reduction.[2,19,26,34]

### 2.3.4. Total cholesterol

Everyone has cholesterol present in the blood, but it is only high levels that pose a risk for CHD. The total lipoprotein containing cholesterol is accounted for in the total cholesterol reading of a lipogram, whereby 60-70% is carried by LDL, 20-30% on HDL, and 10-15% on VLDL. The ATP III concludes that lowering total cholesterol and LDL cholesterol reduces CHD risk (NCEP, 2001) as both have a direct and positive relationship with CHD as mentioned previously (Figure 4).[2,26] There is a U-shape relationship between total or LDL cholesterol and mortality. The optimal ratio of Total Cholesterol: HDL should be 3.5:1 for cardioprotective effects.[15,16,17,21,22,29] Research has found that for each 1% reduction in serum cholesterol, there is a 2% reduction in CHD risk, and that a 10% reduction in total cholesterol would decrease CHD incidence by about 30% (CDC, 2001).[2,22,26]

Total cholesterol levels are increased with age; diets high in total fat, saturated fat, and cholesterol; genetics; endogenous sex hormones; exogenous steroids (anabolic or sex hormones); drugs (β-blockers, thiazide diuretics); body weight; glucose intolerance; decreased physical activity level; diseases (diabetes, thyroid, liver); and season of the year. Increased markers of inflammation (i.e. C-reactive protein) have been found to be associated with lower serum cholesterol levels in HD patients.[4] Dietary adaptation includes substituting SF and trans fatty acids for MUFA and PUFA, and including soluble fibre, soy protein, stanols and sterols, and overall weight reduction like with LDL cholesterol as indicated in the TLC guidelines.[2,19,26,34]

### 2.3.5. HDL

HDL is synthesised and secreted by the liver and the intestine. It is involved in the removal of cholesterol from peripheral tissues to the liver, and it also has other protective effects on the heart and blood vessels

such as antioxidant, anti-inflammatory and anti-clotting effect.[15,16,17,21] Thus high levels of HDL are associated with low levels of chylomicrons, VLDL remnants and LDL cholesterol. It is a strong, negative, independent predictor of CHD incidence and mortality in women and men. Due to the inverse relationship between HDL and CVD risk, a low HDL level is considered to be a strong independent predictor of CHD. HDL can decrease the number and activity of macrophages, which prevents plaque disruption and thrombus formation.[13,35] HDL is increased with exogenous oestrogen (hormone replacement therapy), exercise (>12 weeks with good adherence is more likely to increase plasma HDL in a dose dependant manner), loss of excess body fat, and moderate consumption of alcohol (in particular red wine). Obesity, inactivity, cigarette smoking, androgenic and related steroids (anabolic steroids, progesterone dominant oral contraceptives), β-adrenergic blocking agents, hypertriglyceridemia, and genetic factors decrease HDL cholesterol.[2,6,13,26]

### 2.3.6. Triglycerides

The TG rich lipoproteins include chylomicrons, VLDL, and any remnants or intermediary products formed during fat catabolism (Figure 3).[2,26] The main underlying cause of hypertriglyceridemia is a deficiency of lipoprotein lipase resulting in reduced lipolysis of TG-rich VLDL and enhanced LDL particles with TG. In ESRD levels are increased due to enhanced production and accumulation of TG rich lipoproteins VLDL and IDL. Hypertriglyceridemia alone is a very weak independent risk factor for the development of CHD, but it is almost always found in association with other lipid and lipoprotein abnormalities such as elevated LDL cholesterol and decreased HDL levels. Patients with CHD and familial hypercholesterolemia have higher fasting and postprandial TG levels, necessitating the need to include TGs when doing a lipid profile.[2,6,26,29]

The patient with ESRD rarely has an elevated triglyceride level with or without an increase in cholesterol which may result in pancreatitis (principal focus of treatment). This lipid abnormality likely to represent both increased synthesis of VLDL and decreased clearance (abnormal lipoprotein metabolism).[2,4,26] Diabetic ESRD patients have higher TG and lower HDL cholesterol levels than their non-diabetic counterparts, suggesting that diabetes itself exacerbates lipid abnormalities in patients with renal impairment as mentioned previously.[27]

Levels are increased with β-adrenergic blockers, corticosteroids, oestrogen, alcohol, high carbohydrate diets (especially simple sugars and rapidly hydrolysed starches which are > 60% total energy; i.e. vegetarian, low fat, refined carbohydrate), absorption of glucose from peritoneal dialysate (predispose patients to pancreatitis), the use of heparin (stimulates the action of lipoprotein lipase), decreased hepatic blood flow from cardiac insufficiency, ESRD, nephrotic syndrome, liver disease, untreated diabetes, untreated hypothyroidism, obesity, and a genetic predisposition (familial combined hyperlipidaemia, familial hypertriglyceridemia, and familial dysbetalipoproteinemia). As a result hypertriglyceridemia usually requires weight loss for overweight patients, low fat (25-30% total energy, emphasizing low SF and

cholesterol) diets, decreased intake of refined carbohydrates, increased physical activity, smoking cessation, management of diabetes if present, and abstinence from alcohol.[2,4,6,13,26] In general the TLC guidelines which encompass these factors are applied to patients with hypertriglyceridemia.[4]

### 2.4. EFFECTS OF INDIVIDUAL DIETARY COMPONENTS ON LIPID METABOLISM

Epidemiological and experimental studies, and clinical trials have shown that numerous dietary risk factors affect serum lipids, atherogenesis, and CVD.[2,4,26] Diet is considered essential in modifying the patient's lipid profile, but this does not mean that diet is the sole reason for abnormal readings (Table 7). A diet that emphasises the reduction in total fat, especially that of SF and trans fat, and cholesterol (all in a dose-dependent manner, with the latter having less of a cholesterol-raising effect), promotes the inclusion of fibre, avoid the use of alcohol, include soy protein, considers the inclusion of plant sterols and stanols in the diet, and encourages moderate physical activity to intensify weight management is considered to be cardioprotective. These recommendations are based on data from studies in the general population, and the lack of adverse effects makes a compelling case for recommending them in ESRD patients at risk for ASCVD.[2,,4,19,26,34] Each dietary component will be discussed in more detail (Figure 5).

**Table 7:** Secondary causes of Dyslipidemia [4,17]

| **Medical Conditions** | |
|---|---|
| Obesity<br>Pregnancy<br>Nephrotic syndrome<br>Hypothyroidism<br>Diabetes | Excessive alcohol consumption<br>Liver disease (Biliary obstruction)<br>Diet (saturated/ trans fats, weight gain, anorexia) |
| **Medications** | |
| Anticonvulsants<br>Glucocorticoids<br>Diuretics<br>Beta-blockers<br>Sirolimus<br>Androgens | Oral Contraceptives<br>Corticosteroids<br>Cyclosporine<br>Highly active anti-retroviral therapy<br>Amiodarone |

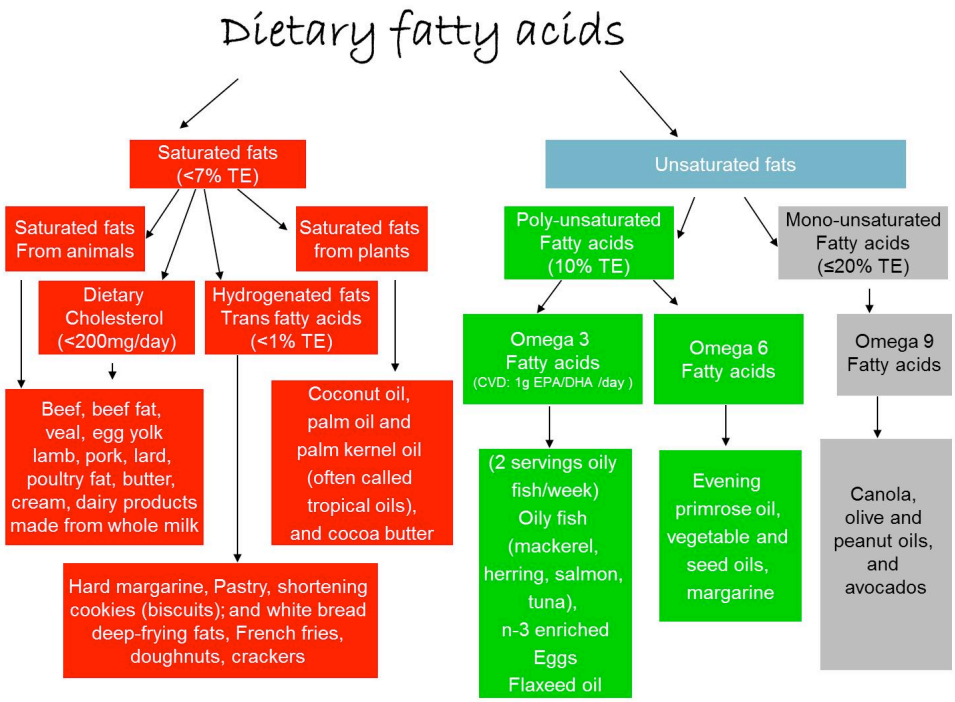



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**Figure 5:** Overview of the various types of fats consumed

### 2.4.1. Total dietary fat

Over 90% of dietary fats are TGs. Other types of fat include cholesterol, phospholipids, sterols, and carotenoids. The functions of fat in the diet are to provide energy (9kcal per gram), essential fatty acids, fat soluble vitamins (vitamins A, D, E and K), increase palatability and appearance of food, used to form biologically active compounds (steroid hormones, interleukins, thromboxanes, and prostaglandins) and constitute cell membranes. Cholesterol is converted to bile acids used for digestion.[15,16,17,21] Fat quantity, fat quality, and cholesterol have been investigated to see how they affect serum lipids and lipoproteins and the resultant atherosclerosis and CVD risk. The quality and quantity of dietary fat to be included in the diet is considered important and supported with Level I Evidence in that it reduces total and LDL cholesterol by 9-16% and decreases the risk of CHD (Table 1).[15,16,17,21,22] Focusing on total fat has been shown to reduce fatty acid intake with subsequent modest improvement in LDL cholesterol level, but no improvement in HDL cholesterol level or other lipid levels. Thus dietary advice regarding both qualitative and quantitative aspects of total dietary fat intake is needed to maximize blood cholesterol-lowering effects.[19] There appears to be no RCTs examining the safety and efficacy of a low fat, low cholesterol diet in patients with ESRD. However, evidence from the general population suggests that a lipid-lowering diet (reduced fat with decreased SF and cholesterol) can reduce LDL cholesterol levels in this population group.[4] Thus the

guidelines from the American Heart Association (AHA, recommends <30% total fat intake) and the ATP IV (25 – 35% with < 7% saturated fat of total energy) are used for this population group.[2,26,36]

### 2.4.2. Saturated fat

Saturated fat has a relatively high melting point and tends to be solid at room temperature. Saturated fat is obtained from animal storage fats and their products (meat fat, lard, dairy, butter) and coconut/palm oil. High intakes of SF increase LDL cholesterol in a dose-response manner by decreasing LDL receptor synthesis and activity, and as a result plasma cholesterol (reduced clearance thereof). Thus excessive intake is associated with atherogenesis and CVD, especially in women.[2,15,16,17,21,26,37] Saturated fat intake is related to disease progression, and reduced intake thereof is related to slower lesion development, promotion of regression of existing lesions, and decreased endothelial dysfunction.[2,26] Saturated fat is more important than total cholesterol intake in affecting serum total and LDL cholesterol levels.[22] For every 1% change in total energy from SF, a 0.05 mmol/L change in LDL cholesterol level is expected.[19] Hence the ATP III guidelines recommending <7% of the total energy coming from SF, as mentioned above.

In general isocaloric replacement of SF with MUFA and α-linolenic acid, and increased fruit and vegetable intake is shown to decrease total cholesterol and LDL cholesterol levels, which collectively reduces CVD events.[2,19,26]

### 2.4.3. Monounsaturated fatty acids

Monounsaturated fatty acids are liquid at room temperature. MUFA are a class of fatty acids that are found in many foods such as olive oil, nuts and avocados. The beneficial effects of MUFA on CVD risk and blood lipid profiles, and as a result the benefits for ESRD patients who are considered at increased risk for CHD, have been extensively studied.[2,26] In particular, dietary MUFA when substituted for SF decrease oxidised LDL cholesterol (amongst other factors e.g. vitamin C and E, β-carotene, selenium, flavonoids, and magnesium), total cholesterol and TG concentrations, without the concomitant decrease in HDL typically seen with low fat diets.[2,26,15,16,17,21] Epidemiological studies done in Mediterranean countries, where high fat diets have been associated with low blood cholesterol levels and reduced CVD incidence. This has possibly been associated, among many other factors (increased intake of fruit and vegetables, fish and nuts; and decreased intake of red meat), with increased intake of MUFA.[2,26] The ATP IV guidelines recommend up to 20% of the total energy intake to come from MUFA.[4,17]

### 2.4.4. Polyunsaturated fatty acids

Polyunsaturated fatty acids (PUFA) are a class of fatty acids that include omega (n)-6 and omega (n)-3 fatty acids. It is liquid at room temperature, and are easily oxidised in foods and in the body. It plays a vital role

in the immune response, blood clotting and inflammation. Epidemiologic clinical studies have shown that PUFA decrease the risk of heart disease when consumed in lieu of SF.[15,16,17,21] The proposed mechanism include reduced plaque growth, decreased platelet aggregation, reduced blood pressure by inhibition of eicosanoid-derived vasoconstriction factors and improved endothelial function, reduced occurrence of arrhythmias, and improved lipid profiles.[6] For every 1% increase in PUFA, a 0.5mg/dL decrease in LDL cholesterol level is predicted.[19] When SF are replaced with complex carbohydrates and/or PUFA in a low fat diet, LDL and HDL cholesterol levels are lowered, whereas when replaced by MUFA and PUFA, LDL cholesterol decreases but HDL cholesterol is unaffected.[2,15,16,17,21,26] An approximate dietary intake of 6% n-6 and 1% n-3 fatty acids as percentage of total energy (total of 10% total fat intake) has been recommended to maximise the cardiovascular benefits of these essential fatty acids.[4]

### 2.4.5. Omega-6 fatty acids (18:2 / Linoleic acid)

Major sources of n-6 fatty acids include those of vegetable oils, salad dressings, and margarine made with the oils. It is well established that n-6 fatty acids lower blood cholesterol concentrations compared to other more saturated types of fatty acids or carbohydrates.[38] Western diet contains a high ratio of n-6:n-3 PUFA, a lower ratio (4:1) is recommended to improve cardiovascular risk factors.[15,16,17,21]

### 2.4.6. Omega-3 fatty acids (18:3 / Linolenic)

Omega-3 fatty acids are found in oily fish and fish oils. The n-3 fatty acid is a precursor for two main forms, namely docosahexanoic acid (DHA) and eicasapentanoic acid (EPA).[2,15,16,17,21,26] Beneficial effects of EPA and DHA include: 1) decreased plasma TG, free fatty acids, glucose and insulin; 2) prevention of peripheral insulin resistance; 3) decreased TG concentrations, VLDL secretion and utilisation and storage of glucose in skeletal muscle; 4) decreased adipocyte cell size and visceral fat content and increased insulin-stimulated glucose transport in the adipose tissue; 5) decreasing platelet adhesion; 6) decreasing vasoconstriction; 7) reducing inflammation; and 8) decreasing ventricular arrhythmias by modulation of cardiac ion channels. As a result increased consumption thereof is known to improve cardiovascular risk factors, by lowering cholesterol, LDL, and TG levels.[2,15,16,17,19,21,26] Evidence from epidemiologic and RCTs report omega-3 fatty acids to decrease CVD risk, and notably the risk of sudden death and other cardiac events. Thus it will have the same beneficial effect in patients with ESRD. Food sources of omega-3 fatty acids include cold water fish (mackerel, salmon, herring, trout, sardines and fresh tuna) which contain EPA and DHA, and those containing short chain omega-3 fatty acid (ALA, less bioavailable as <1% is converted to DHA in humans) like flaxseed, walnuts, canola oil and soybeans. The AHA recommends 1g EPA plus DHA per day for individuals with CHD, and up to 3 g/d to reduce the risk thereof under a clinician's supervision. Most of these foods are high in phosphate, and or extremely expensive for most individuals, which limits the inclusion thereof in the general or renal populations diet.

### 2.4.7. Trans fatty acids

The most significant source of trans fatty acids in the diet is obtained through the hydrogenation of PUFA to produce more solid forms of vegetable oils for spreads, margarines, and some food products.[15,16,17,21] Intake of trans-10, cis-12 conjugated linoleic acid from hydrogenated oils has been found to increase systemic inflammatory markers, induce endothelial dysfunction, and unfavourably alter the blood lipid profile by increasing the LDL:HDL and total cholesterol:HDL ratios. Trans fatty acids increase LDL to a lesser extent than saturated fat, but are still considered atherogenic.[2,15,16,17,19,21,22,26] A recent meta-analysis found that trans fatty acids increased total cholesterol/ HDL cholesterol ratio almost twice that of SF at a comparable dose. As a result replacing 10% of energy from butter with soft tub margarine (typically 3.3% trans fatty acid content) low in trans fatty acids (versus stick margarine high in trans fats, typically 6.72% trans fatty acid content) decreased total cholesterol by 9.7 mg/dL and LDL cholesterol by 7.7 mg/dL respectively; had no effect on HDL cholesterol levels; and decreased total cholesterol/ HDL cholesterol ratio by 7.7 mg/dL. This meta-analysis emphasised the importance of reducing both SF and trans fatty acid and replacing them with MUFA and PUFA for the most favourable results.[19]

### 2.4.8. Dietary cholesterol

Dietary cholesterol raises total cholesterol and LDL cholesterol to a lesser extent than SF and trans fatty acids.[2,26] On average, an increase of 100 mg/day of dietary cholesterol results in a 2-3 mg/dL increase in total serum cholesterol, of which 70% is in the LDL fraction. A diet low in SF, and trans fatty acids, and cholesterol would be expected to lower LDL cholesterol by 11-15% and possibly by as much as 20%.[6] The intake of cholesterol has generally been positively related to the risk of CVD after adjusting for other risk factors, such as age, blood pressure, serum cholesterol level, and cigarette smoking. There is a threshold for a plasma cholesterol response to dietary cholesterol (<500 mg/d).[2,26]

### 2.4.9. Plant sterols and stanols

Cholesterol and cholesterol esters are found in animal foods and phytosterols are found in plant foods. They are chemically related and structurally similar to cholesterol, but are not synthesised by the human body.[19,38,39] Plant sterols and stanols (phytosterols) are isolated from soybean oils or pine tree oil. As early as the 1950s, plant sterols and stanols have been known to lower LDL cholesterol.[2,15,16,17,21,26,34,40,41,42] Plant sterols and stanols are esterified to unsaturated fatty acids to facilitate maximal incorporation into small amounts of fat (enter into micelles as they are more hydrophobic), blocking intestinal absorption of dietary and biliary cholesterol which are needed for cholesterol to dissolve (Figure 4). Consequently inhibiting cholesterol absorption as endogenous and dietary cholesterol become insoluble and as a result are excreted in the stool. This suggests that plant stanols and sterols lower LDL by reducing the number of particles being absorbed rather than the size or composition thereof. The absorption of fat-soluble vitamins is not significantly affected. This was seen in numerous studies where after adjustments were made for

reductions in total and individual lipoprotein cholesterol levels, vitamin concentrations were unaffected. Phytosterols themselves are not absorbed or excreted well.[4,6,19,25,32,34,39,42] Recently there has been some concern regarding serum levels of plant sterols and the risk of CVD, as it was found that plasma plant sterol concentration will increase after plant sterol consumption and later undergo oxidation to form oxyphytosterols which are considered to be atherogenic in *in vitro* and animal studies. In phytosterolemia (a rare genetic disease), severe loss of function mutations in genes coding for the ABCG5/ABCG8 transporters result in dramatic elevation in plasma plant sterol levels, which are more than 50-fold higher than those in normal individuals after consumption of plant sterols, and many of these individuals develop premature atherosclerosis. The reduction in serum cholesterol levels is achieved at the expense of increased serum plant sterol levels. This being so, the study by Baumgartner et al stated that daily consumption of plant sterol-enriched margarine does not increase oxyphytosterol concentrations, and a recent systemic review failed to show any evidence for an association between serum levels of plant sterols and risk of CVD (17 studies involving 11182 participants). [20,43,44,45,46,47] Evidence from clinical studies and post launch-monitoring indicates that overconsumption of foods with added plant sterols is not an issue and can be encouraged. Hence the European Atherosclerosis Society also refuted the emerging safety issues, and a consensus panel concluded that plant sterols can be used in those requiring lower LDL cholesterol levels and in persons at increased risk for CHD.[20,45,46,47,48] They are generally well tolerated, and no adverse effects have been noted with up to 9 g/day for eight weeks, or with lower doses given for a longer time period.[49]

Randomised control trials have demonstrated cholesterol-lowering effects of esterified plant sterols and stanols in both normocholesterolemic and hypercholesterolemic individuals, and a recent meta-analysis of six studies including such individuals reported a 7-11% decrease in LDL cholesterol after four 4 weeks to three months of intervention.[19] In general they reduce cholesterol levels in a dose dependant manner by 4-11% and LDL cholesterol concentrations by 15-20% without changing HDL and TG concentrations (Level I Evidence).[15,16,17,21,22] Phytosterols are the only functional food/supplement with moderate effectiveness when compared to fibre, soy protein, n-3 fatty acids etc.[6,34,42] In general phytosterols are shown to significantly reduce total cholesterol:HDL cholesterol ratios; and decreases were more pronounced in participants with higher baseline values. In patients with low baseline HDL cholesterol concentrations, HDL cholesterol was slightly increased, while in patients with high baseline concentrations, it was marginally lowered. This slight reduction would not increase cardiovascular risk, because at the same time, LDL cholesterol would be decreased substantially. In previous meta-analyses by Law et al (2000) and Katan et al (2003), older patients showed larger reductions in LDL cholesterol levels.[41] It was hypothesised that this effect was due mainly to the higher baseline LDL cholesterol concentrations with increasing age.[41]

Thus evidence is sufficient to promote the use of sterols and stanols for lowering LDL cholesterol levels in persons at increased ASCVD risk. The question remains how best to optimise their use in lipid management.[20] Miettinen et al (1998) indicated that by including phytosterol-enriched margarine for a portion of normal dietary fat is suitable as a strategy to reduce plasma cholesterol levels.[38] A meta-analysis of 41 trials showed that intake of 2-3 g of phytosterol ester enriched fat-based foods like spreads, margarines, mayonnaise, or salad dressings, should be consumed on a daily basis for at least three weeks, to lower cholesterol (by 9-20% or -0.35 mmol/L) and LDL cholesterol (6-15% reduction), even with those patients currently receiving statins, according to the ATP IV recommendations.[4,6,32,17,41]

Various studies have demonstrated a dose-response effect with a step-wise reduction in LDL cholesterol with increasing doses of 0.8, 1.6, 2.4, and 3.2 g of plant stanols; however, the differences in cholesterol reduction between the higher doses (2.4 and 3.2 g/d) were not statistically significant. These data suggest that a dose of 2 g/d is optimum.[6,34,45,50] Intakes higher than 2 g add little effect, and therefore are not recommended. The cholesterol-lowering effect reaches a plateau with increasing doses due to the saturable nature of the processes involved in cholesterol transport and absorption.[32,41,51] Level II Evidence supports that 2-3 g per day are considered to be generally safe. [15,16,17,21,22,34,45,50,52,53] Maximum changes after initiating use of plant sterols are observed after two weeks and these effects are sustained in the long term provided compliance is maintained.[54] Previous studies have also found that the serum cholesterol concentrations return to initial value within two to three weeks once the enriched margarines have been stopped.[55] Effects are additive with diet or drug interventions (closer to 20% reduction in LDL may be noted). Even if unhealthy diets are followed, sterols and stanols will lower cholesterol levels. But generally speaking, sterols and stanols should complement a healthy diet as indicated by the NCEP ATP IV (TLC, get a further 5% reduction). Studies have shown that adding sterols and stanols to drug therapy (i.e. statins) of dyslipidemia may appear more effective than doubling the dose of the drug. This was shown in a study where 22 women with CAD consuming 3 g/day sitosterol-enriched margarine as part of a fat-modified diet for seven weeks produced a reduction in total cholesterol of 13% ($P<0.05$) and LDL cholesterol of 20% ($P<0.01$). The addition of simvastatin therapy further reduced these levels with an additional 11% and 16% respectively. The authors of this study also suggested that the combination of sitosterol and a statin may reduce the dose of the cholesterol-lowering drug needed, and beyond the use of statin therapy alone.[19] This may be beneficial in ESRD patients who are at increased risk for complications associated with drug therapy.[32,41]

Epidemiological studies in the UK (n=22256), Sweden (n=77652, NORDIET) and China (n=3940) observed that naturally occurring plant sterol intake is inversely related to plasma total cholesterol and LDL cholesterol levels. In another well-controlled study of healthy participants, even at the highest concentration of dietary intake (449mg/2000kcal), plant sterols occurring naturally in the diet have a

modest hypocholesterolemic effect. On the other hand when these foods were omitted from the diet, LDL cholesterol concentrations increased. Subsequent data has shown consistent support for the LDL cholesterol-lowering effects of foods with added plant sterols in the management of dyslipidemia versus consuming natural dietary sources alone.[20,56]

There are no contraindications to the use of phytosterols in patients with ESRD; however, they should be used as a fat substitute so as to have no adverse effects on weight or other risk factors.[4,5] More studies are needed to clarify the specific effects of dietary components such as sterols and stanols on the health of these patients. Current data regarding the use of data of stanol and sterol esters are now available for up to two years in the United States and Europe, and over five years in Finland, and no adverse effects have been reported. According to the updated ESC/EAS guidelines they can be safely recommended to lower LDL cholesterol in those at risk of ASCVD as mentioned previously.[6,32] The problem with these products is that they are generally more expensive and not all are appropriate for renal patients (sunflower kernels, pistachio nuts, wheat germ, fortified yoghurts, orange juice, etc.), owing to their potassium and phosphate content. Processed plant sterol esters (esterified to make them more soluble in dietary fat, thereby promoting their efficacy) have been incorporated in commercially available margarine spreads in the UK since the late 1990s; these margarines can be used by this subgroup of patients (Table 8).[2,4,22,26,32,42,57] The optimal dose of sterol/stanol from margarines is consumed with 25 g of fat (providing 2.5 g of phytosterols).[32,42,58]

**Table 8:** Energy and nutrient composition of margarines.[54]

| | Standard spread | Plant sterol spread | Extra light spread |
|---|---|---|---|
| **Energy (kJ/100g)** | 2605 | 1348 | 1367 |
| **Total fat (g/100g)** | 70 | 35 | 35 |
| **[a]SF (%total fat)** | 24 | 8 | 8 |
| **[b]MUFA (%total fat)** | 32 | 7 | 7 |
| **[c]PUFA (%total fat)** | 43 | 19 | 18 |
| **Cholesterol (mg/100g)** | 0 | 0 | 0 |
| **Plant sterols (mg/100g)** | 400 | 8000 | 400 |

*Analysis supplied by manufacturer (Unilever)*

*[a]SF Saturated Fat; [b]MUFA Monounsaturated Fatty Acids; [c]PUFA Polyunsaturated Fatty Acids*

The fat content of the food format (fat-based versus non-fat-based) and the type of phytosterols (plant sterols versus stanols) does not significantly affect the absolute and relative dose-response curves in some previous studies. However other studies have found that the effect of phytosterol formulation is important.[41] The effects of dimethylsterols from rice bran on lipoproteins are less than those of sterols

derived from cholesterol such as sitosterol. The other significant effect of food format of these phytosterol ester enriched foods is solid versus liquid. A previous study found that, at high doses, the maximal estimated LDL cholesterol-lowering effect of solid foods enriched with these esters was 5.2% greater than that of the liquid form, an effect possibly related to the longer transit time in the gastrointestinal tract.[32,34,41,45,59] It was previously stated that it is not necessary to consume phytosterols simultaneously with dietary cholesterol or with each meal, as it was hypothesised that they remain in the intestinal lumen, or possibly in or associated with the enterocytes. Recently Doornbos et al suggested that the fat and protein content of a consumed meal determines the effectiveness of the plant sterol as it triggers the release of cholecystokinin after a meal, thereby causing secretion of bile, a necessary step in the formation of mixed micelles. Hence the findings suggest a fed state is necessary for an optimal cholesterol-lowering activity, as this induces bile flow and the release of pancreatic lipase. This indicates that replacement of intestinal cholesterol from the micelles is not the only mechanism of action by which plant sterols lower LDL cholesterol, but rather that biliary cholesterol absorption in the intestine is also suppressed.[25,34,59] More trials to compare the efficacy and effectiveness of different dosing regimens are required, to examine the effect on the need for cholesterol-lowering medications, and to evaluate the potential bioavailability of nutrients in foods, beverages and supplements.[19,32] With the exception of phytosterols and n-3 fatty acids, most supplements have demonstrated only a small beneficial effect on blood lipids compared to that of traditional pharmaceutical agents.[6]

### 2.4.10. Fibre

Dietary fibre can be classified as soluble or insoluble, and according to this classification it is given different functional categories. Insoluble fibre consists mainly of cellulose and some hemicelluloses. It binds to water in the colon and swells, reducing the risk of constipation by increasing transit time in the colon. Soluble fibre (pectins, gums, mucilages, algal polysaccharides, and some hemicelluloses in legumes, oats, fruits and psyllium) blunts the response of blood glucose to food intake and slows the reabsorption of bile acids resulting in increased cholesterol losses in the faeces and the resultant decrease in cholesterol levels (Figure 3). This being said soluble fibre appears to have greater LDL cholesterol-lowering potential than insoluble fibre, but observational data and meta-analysis conclude that high total fibre intake remains inversely related to CHD, reduces all cause dietary and CVD mortality. [19,34] Level I Evidence suggests that by increasing ones fibre intake total cholesterol may be decreased by 2-3% and LDL cholesterol by 7%, albeit SF and cholesterol are also reduced. Soluble fibre has more of an effect than insoluble fibre, thus 7-13 g of the 25-30 g of total fibre requirement per day should come from soluble fibre. By including this amount of soluble fibre per day it is expected that LDL cholesterol levels will be reduced by 3-5%. The hypocholesterolemic effect of soluble fibre is as a result of 1) the fibre binds to bile acids lowering serum cholesterol to complete the bile acid pool; and 2) bacteria in the colon ferment the fibre to produce acetate, propionate, and butyrate, which inhibit cholesterol synthesis.[2,6,19,22,26] In general fibre lowers blood

cholesterol (mainly soluble fibre), attenuates TG levels (mostly soluble fibres), decrease hypertension (all fibres), and normalise postprandial blood glucose levels (all fibres). An increased intake of fibre is especially important in CAPD where uptake of dialysate glucose may increase risk of hypertriglyceridemia and poor glucose tolerance.[4,5,15,16,17,21] The problem with high fibre diets is that they require additional fluid intake. This may be difficult for the anuric dialysis patient who is often restricted to 1 L of fluid per day. Many high fibre foods are also restricted in the renal diet owing to their high phosphorus and/or potassium content.[4,5]

### 2.4.11. Alcohol

There is a dose dependant effect of alcohol intake and total TGs. Moderate alcohol (maximum of one drink per day for women and up to 2 drinks per day for men as part of a cardioprotective dietary pattern within recommended energy levels) consumption, especially of red wine (contains resveratrol a phenolic antioxidant, 150ml), is associated with decreased risk of myocardial infarction and CHD mortality as it increases HDL cholesterol and inhibits LDL oxidation.[2,26,60] Alcohol is generally prohibited with ESRD patients especially that of red wine owing to its potassium levels. No studies on the effects of alcohol consumption in patients with ESRD have been done.[4,5]

### 2.4.12. Soy protein

There is a dose-response relationship between soy protein and blood lipid levels. Overall, a daily intake of 25 g of soy, with isoflavones intact, will lower LDL cholesterol by 4 to 8 % in hypercholesterolemic persons and thus reduces the risk of CVD.[2,26,61]

## 2.5. CURRENT DIETARY GUIDELINES

Managing heart disease requires a healthy cardioprotective diet[22]. There are no cardioprotective dietary guidelines specific to dialysis patients.[29] Renal impairment may conflict with the principles of the cardioprotective diet, so advice must be given holistically to take into account the likely prognosis. Dietary management should be based on the nutritional assessment finding; and general population guidelines are used (Table 9), such as the TLC guidelines for this subgroup of patients.[4,5,15,16,17,21,27] It must be emphasised that the guidelines mentioned below and in Table 9 are not to replace clinical judgment, but rather to guide and inform decision-making, as with all other guidelines.

**Table 9:** Summary of dietary guidelines used with ESRD patients receiving RRT for prevention of dyslipidemia

| | AHA & ACC | NHLBI NCEP ATP IV | | TLC (ATP III) | NKF-K/DOQI | KDIGO | | ESC/ EAS | SA lipid |
|---|---|---|---|---|---|---|---|---|---|
| **Primary Treatment (Lifestyle modifications)** | Avoid tobacco | Follow an ANTI-atherogenic diet (Step I & Step II) | | Follow an ANTI-atherogenic diet (similar to Step II) | ***Follow an ANTI-atherogenic diet (TLC)*** | ***Change diet using kidney specific strategies recommended by NKF-KDOQI guidelines*** | | Follow an ANTI-atherogenic diet | Avoid smoking |
| | Maintain a healthy weight | Maintain a healthy weight | | Maintain a healthy weight using BMI & WC | ***Maintain a healthy weight using BMI & WC*** | ***Maintain a healthy weight using BMI ($kg/m^2$) according to country specific demographics, using frame size*** | | Include physical activity (30min 3x/week) | Include physical activity (30min/day) |
| | Include physical activity | Include physical activity | | Include physical activity (low intensity) | ***Include physical activity (motion & distance within patients ability; 3-4x/week for 20-30min; include 5min warm up & cool-down; include cardio & resistance training; and emphasize lean muscle mass & decreased fat mass)*** | ***Include physical activity (compatible with cardiovascular health & tolerance, min 30min 5x/week)*** | | | Make healthy food choices (prudent dietary guidelines) |
| | | | | | ***Avoid smoking*** | ***Avoid smoking*** | | Avoid smoking | |
| | | | | | ***Limit alcohol intake to <1/day, if consumed*** | | | Limit alcohol intake to <10-20g/d for females & <20-30g/d for males, if consumed | |
| **Secondary treatment** | ***Medication:*** Fibrates, Niacin, Statins | | | | | | | | |
| **Focus / Target of treatment** | Increased cholesterol, blood pressure, & body weight | Decrease CHD risk related to dyslipidemia, especially LDL cholesterol & TG levels | | Decrease CHD risk by improving LDL and HDL cholesterol levels | ***Control dyslipidemia (especially LDL cholesterol), blood pressure control, weight loss if necessary, & reduce protein to recommended levels*** | ***Control dyslipidemia, blood pressure, & hyperuricemia*** | | Reduce total cholesterol & LDL choelsterol levels, blood pressure & blood glucose levels to reduce cardiovascular mortality | Based on EAS |
| **Diet** | | | | | | ***Differs according to RRT received*** | | | |
| | <30% TE from FAT | Step I<br><30% TE from FAT | Step II<br><30% TE from FAT | (Step II) | ***25-35% TE from FAT*** | ***HD<br>30-40%TE (closer to 30% optimal)*** | ***PD*** | 25-35% TE from FAT | Substitute full fat with low fat / fat free similar choices |
| | Limit trans fats | | including that of trans fat within the 7% SF | | ***<1% trans fat*** | | | <1% trans fat | Use plant oils rather than butter / animal fat / coconut / palm oil |
| | <10% SF | SF:MUFA <10%:10% | SF <7% | | ***SF:PUFA:MUFA <7%:10%:20%*** | ***SF:PUFA:MUFA <10:<10:>10%*** | | SF:PUFA:MUFA <7:<10:>10% | |
| | <300mg/d dietary cholesterol | <300mg/d dietary cholesterol | <200mg/d dietary cholesterol | | ***<200mg/d dietary cholesterol*** | ***<300mg/d dietary cholesterol*** | | <300mg/d if hypercholesterolemia present | Modify cooking methods (no frying) |
| | Consume fish 2x/week | | | Decrease intake of sodium rich foods (<2400mg NaCl/d) | ***Total energy to attain & maintain NHANES body weight*** | ***Total energy intake if <60years: 35kcal/kg, or if > 60years: 30-35kcal/kg (both excl that from dialysate)*** | | Total energy adjusted to prevent overweight / obesity | Avoid simple carbohydrates |
| | Avoid simple sugars | | | Increase consumption of fruits, vegetables & fibre | ***50-60% TE from Complex carbohydrates, with 20-30g Fibre intake (5-10g from soluble fibre)*** | ***50-60% TE from Complex carbohydrates with 20-25g Fibre intake*** | | 45-55% TE from Complex carbohydrates (<10% from sugar) | Increase intake of fruit & vegetables |
| | Consume more low glycemic index foods | | | 2-3g/d Plant sterol & stanol can be consumed | ***2g/d Plant sterol & stanol can be consumed*** | ***1.2g/kg Protein per day*** | ***1.3g/kg Protein per day*** | Decrease intake of sodium rich foods (<2400mg NaCl/d) | Avoid high fat protein (especially processed versions thereof) |
| | | | | | | | | Varied diet to be consumed to provide sufficient & variety of antioxidants | Avoid / limit alcohol intake |
| | | | | | | | | 1-2g/d Plant sterol & stanol can be consumed if total & LDL cholesterol levels are increased | |

*AHA / ACC: American heart association and the American colledge of cardiology; NHLBI / NCEP ATP IV: National Heart, Lung, and Blood Institute's and National cholesterol education program adult treatment panel; TLC: Therapeutic lifestyle change; NKF-K/DOQI: National kidney foundation Kidney/ disease outcome quality initiative; KDIGO: Kidney disease improving global outcome; ESC/ EAS: European society of cardiology and European atherosclerosis society*

*BMI: Body mass index; WC: Waist circumference; CHD: Cardiac heart disease; LDL: Low density lipoprotein; TG: Triglycerides; RRT: Renal replacement therapy; HD: Hemodialysis; PD: Peritoneal dialysis; TE: Total energy; SF: Saturated fat; MUFA: Monounsaturated fat; PUFA: Polyunsaturated fat*

*According to KDIGO guidelines a Healthy weight for ESRD patients is a BMI of 20-25kg/$m^2$, depending on their frame size (small frame size - aim for lower BMI vs large frame size - aim for higher BMI).*

*Healthy weight in dialysis patients according to KDOQI guidelines and Kamyar Kalantar-Zadeh BMI of 27 associated with improved survival*

### 2.5.1. American College of Cardiology (ACC) and the American Heart Association (AHA)

The American college of cardiology and the American heart association (ACC/AHA) guidelines-derived from randomised trials, meta-analyses and observational studies evaluated for quality-emphasises lifestyle modification that includes avoidance of tobacco products, maintenance of healthy weight, and 'heart healthy' patterns of dietary intake and physical activity for the promotion of cardiovascular health and prevention of dyslipidemia and other risk factors for cardiovascular disease. The guidelines focus on the three main risk factors associated with heart disease: increased blood cholesterol, increased blood pressure, and excess body weight. The guidelines were recently updated (2013), and the focus was specifically directed on treatment of blood cholesterol to reduce atherosclerotic CVD risk. Guidelines, and problems associated with each, include the following:

- Treat to target. A problem with this widely used approach is that clinical trial data does not indicate what the target should be. If treatment is targeted, it is unknown whether this will result in greater atherosclerotic CVD risk reduction versus what would be achieved with one target lower than the other. The approach also does not take into account potential adverse effects from multidrug therapy that might be needed to achieve a specific goal. Future clinical trials may provide information warranting reconsideration of this strategy.
- Any reduction in lipid level is more beneficial than none. This approach does not consider the potential adverse effects of multidrug therapy with an unknown magnitude of atherosclerotic CVD event reduction, as mentioned above. On-going RCTs of new drugs in the setting of maximal statin therapy may address this strategy.
- Benefits of treatment should outweigh the side effects thereof.–There are four statin benefit groups (shown to be more practical and simpler to implement), and important exceptions for routine initiation of statin treatment include individuals requiring hemodialysis or with class II-IV NYHA.
- Lifetime risk of atherosclerotic CVD is the last approach. Lack of data on the long-term follow up of RCTs >15 years, the safety and atherosclerotic CVD event reduction when statins are used for periods >10 years, and treatment of individuals <40years of age is found to be problematic.

Basic guidelines recommended by the ACC/AHA for achieving desirable blood lipid profile and especially LDL cholesterol levels can be seen in Table 9.[17,38] The updated guidelines found no atherosclerotic CVD outcomes identified for plant sterols, sterol esters, stanols, or stanol esters.[17] These guidelines are not stringent enough for ESRD patients at risk for dyslipidemia.

### 2.5.2. The National Heart, Lung, and Blood Institute's National Cholesterol Education Programme Adult Treatment Panel IV

The National Heart, Lung, and Blood Institute's (NHLBI) National cholesterol education programme (NCEP) has been developing guidelines for reducing the incidence of CHD in the general population since 1985. NCEP periodically produces adult treatment panel (ATP) clinical updates as warranted by advances in the science of cholesterol management (it was recently in 2013). The ATP IV document is an evidence-based and extensively referenced report that provides the scientific rationale for the recommendations contained in the executive summary.[9] It aims at lowering the CHD risk related to dyslipidemia, whereby LDL cholesterol and TG levels are targeted. The recommendations are intended to provide a strong evidence-based foundation for the treatment of cholesterol for the primary and secondary prevention of atherosclerotic CVD in men and women. Features of ATP III include (1) raising diabetes as an important risk factor for CVD; (2) using Framingham projections of 10-year absolute risk to identify patients for more intensive treatment; and (3) identifying persons with multiple metabolic risk factors as candidates for intensified TLC. Keep in mind that the Framingham risk equation is said to underestimate true events in a CKD population, but no other different validated tools exist at present which better quantify cardiovascular or mortality risk in the CKD population. The guidelines established a central, causal role of atherogenic cholesterol-containing lipoprotein particles, particularly LDL, in the genesis of CHD and atherosclerotic CVD; they determined other strategies for using drug therapy to reduce atherosclerotic CVD risk (as mentioned above). These guidelines are applied to dialysis patients, because of their high risk for the development and progression of atherosclerosis and CVD; and because it is prudent that a cautious treatment approach be taken in the treatment thereof as these persons are prone to drug side-effects (increased risk of myopathy from both fibrates and statins). Diet therefore remains a primary prevention/treatment thereof both prior to and in concert with the use of cholesterol-lowering drug therapies.[4,5,17,26,61]

The ATP III separates other CVD risk factors into lifestyle factors (obesity, physical inactivity, atherogenic diet), which constitute the intervention areas; and the emerging risk factors (lipoprotein (a), homocysteine, prothrombotic and proinflammatory factors, and impaired fasting glucose) guide decisions regarding the intensity of risk reduction therapy.[2,5,26] Age, lifestyle habits (smoking and body mass index (BMI)), and total cholesterol showed a positive association with CHD morbidity and mortality. The dietary intervention consisted of the Step I and Step II diets.

The aim of the Step I diet was to prevent CHD in individuals with LDL cholesterol concentrations ≥4.14 mmol/L (Table 2) and ≥ two risk factors (cigarette smoking, hypertension, decreased HDL, family history of premature CHD, and ≥45-year-old males and ≥55-year-old females) shown in Table 9. Both the Step I and AHA guidelines recommend high fat and MUFA, and both are equally effective in lowering total cholesterol and LDL cholesterol levels, without influencing HDL cholesterol. This diet may be more cost effective, and being a less restrictive diet, it may better meet the patient's caloric needs. The problem with this diet is that clinical trials have shown new atherosclerotic lesions similar to those seen with diets high in SF.[2,25,26,60,61,62,63] Step II, updated and renamed the TLC diet (used in ESRD patients) is more restrictive (Table 9), and uses LDL cholesterol as the primary goal of therapy.

### 2.5.3. Therapeutic lifestyle change

Adult Treatment Panel III recommends a multifaceted lifestyle approach to reduce risk for CHD, contained in the TLC guidelines. A therapeutic lifestyle modification programme is effective as a nutrition and physical activity intervention and has the potential to reduce the risks associated with CHD by improving LDL and HDL cholesterol levels (NHLBI, 2001).[13,19,64] In addition to the TLC diet (Table 9), the nutrition education of the cardiac patient should focus on: changing modifiable risk factors; the importance of achieving a healthy weight (NHANES, National Health and Nutrition Examination Survey), BMI and waist circumference (by reducing overall calorie intake especially for PD patients); increasing regular low-intensity physical activity (walking); appropriate macronutrient consumption with increased intake of fruit, vegetables and high fibre foods; the importance of reducing sodium intake (<2400 mg per day NaCl, increased intake thereof is related to higher concentration of glucose in the dialysate being needed to help avoid volume overload); and including therapeutic options for enhancing LDL lowering with the inclusion of 2-3 g per day plant sterols and stanols in the diet.[15,16,17,21,22] Second line therapies (pharmacological agents) for those where TLC was unsuccessful in controlling dyslipidemia, are recommended. Dyslipidemia, specifically elevated LDL cholesterol levels, is one of the most important modifiable risk factors, which requires the use of the cardioprotective diet and lifestyle modification.[2,23,24,26] The first step in the selection of LDL-lowering therapy is to assess a person's risk status. This helps to determine the need for TLCs and the level for drug consideration (secondary prevention) where TLC alone may prove unsuccessful. For patients with near or above optimal (2.59-3.34 mmol/L) LDL levels, it is reasonable to attempt TLC dietary changes for two to three months before beginning drug treatment.[4,65] The diet is based on several well-established behaviour change models that aim to lower LDL cholesterol in the population whose LDL cholesterol is above the goal level for its category of risk for heart disease.[22,23,24] Behaviour outcomes include appropriate meal planning, food label reading,

knowledge of the soluble fibre content of the foods, recipe modification, food preparation, dining out, and food-drug interactions.[2,26]

### 2.5.4. National Kidney Foundation-Kidney/Disease Outcome Quality Initiative

The NKF-K/DOQI convened a work group in 2000, to develop guidelines for the management of dyslipidemias, one of the risk factors for CHD, in ESRD. These guidelines were adopted from the NCEP ATP IV as mentioned previously.[4] The NKF-K/DOQI guidelines recommend that counselling interventions include aggressive blood pressure control, reduction in dietary protein to recommended levels, weight loss and control of hyperlipidemia.[66,67] Macronutrient requirements as specified by the NKF-K/DOQI guidelines for dialysis are shown in Table 9.[15,16,17,21] Evidence from controlled trials is mostly lacking; thus, where possible, general healthy eating guidelines are recommended.[15,16,17,21]

K/DOQI guidelines and the NCEP ATP IV guidelines indicate that all adults with ESRD should be evaluated for lipid abnormalities, and the main focus of treatment is the level of LDL cholesterol as dialysis patients are in the highest risk group for CVD events.[5,27] LDL levels as low as 2.6 mmol/L for non-diabetics and 1.8 mmol/L for diabetics are advocated.[67] The NKF/KDOQI guidelines for managing this dyslipidemia suggest that ESRD patients who are known to have impaired lipoprotein metabolism be treated with TLCs followed by a statin, to achieve a normal lipid profile.[4,5,22,27,30,68,69]

### 2.5.5. Kidney disease improving global outcomes

The KDIGO clinical practice guidelines task force acknowledges that all patients with CKD should be considered at increased risk for CVD as seen by K/DOQI. Interventions to reduce hospitalisation and mortality of patients with CKD should pay close attention to the management of associated comorbid conditions and CVD in particular (CKD is an independent risk factor thereof). The clinical update from KDIGO regarding CVD in CKD was done in 2011, and it aims to offer best practice and evidence-based advice on the evaluation and approach to management of CKD in an international context, sensitive to issues related to ethnicity and also geographical considerations.[5] Risk reduction thereof includes management of hypertension, dyslipidemia, and hyperuricemia. KDIGO encourages physical activity (aiming for at least 30 minutes five times per week), the achievement of a healthy weight (BMI 20-25kg/$m^2$ according to country specific demographics), changing diet using kidney-specific dietary strategies, and to discontinuing smoking. The 2013 KDIGO clinical practice guidelines for lipid management in CKD, in particular for dialysis dependant recipients assessment and treatment for dyslipidemia is comprehensively discussed. These guidelines recommend that follow

up assessment of lipid levels (total cholesterol, LDL cholesterol, HDL cholesterol, TG) is not required for the majority of CKD patients (not graded). They rather recommend a 'fire and forget' strategy where only if treatment management will result in a change, should these levels be retested to monitor adherence to treatment or other processes of care. There is no direct evidence that routine follow-up of lipid levels improves clinical outcomes or adherence to lipid lowering therapy, but rather that there is inpatient variance in serum total cholesterol levels (±0.8mmol/l) and therefore this measurement does not reliably indicate good or poor compliance. However physicians can choose to perform a follow up measurement based on favourably influencing patients compliance based on this knowledge thus positively influencing their process of care. An example of such a scenario would be with a patient that is >45 years of age with CKD stage IV, who is a non-smoker without diabetes or hypertension as their predicted 10-year risk of coronary death or MI could vary from 5-20% based on cholesterol level. As discussed above under the ACC/AHA guidelines, the 'treat to target' is not recommended as there is no proven benefit seen in clinical trials suggesting this, and in addition higher doses of statins have not been proven to be safe in CKD patients. Hence those with dyslipidemia (not based on secondary causes of dyslipidemia identified after dialysis has been already initiated should not be given a statin or statin / ezitimibe combination (level 2A); and those already receiving statins or statin / ezitimibe combination at time of dialysis initiation should be continued (level 2C appraisal – suggested based on low evidence). Despite the exceedingly high cardiovascular risk in dialysis patients, it is uncertain whether statin regimens lead to direct clinical benefit in this population; the recommendation for statin therapy is weak as there is a small potential relative reduction of cardiovascular events and a relatively high risk of polypharmacy and drug toxicity.[5]

In general, expert dietary advice and information should be given to all CKD patients in the context of an education programme, tailored to the severity of CKD and the need to intervene on salt (<2 g/d Sodium / <5 g/d Sodium Chloride), phosphate, potassium, protein, and dietary fat intake (using the TLC guidelines) where indicated by a qualified dietician (Table 9).

### 2.5.6. The European Society of Cardiology and European Atherosclerosis Society

The European Society of Cardiology and European Atherosclerosis Society (ESC/EAS) task force recommends stronger action when it comes to measuring cholesterol levels in at risk patients. Prevention and treatment of dyslipidemias should always be considered within the broader framework of CVD prevention. Evidence from RCTs shows that reducing total cholesterol and LDL cholesterol can prevent CVD, thus they constitute the primary targets of therapy. Patients with CKD

are also at increased risk for CVD and should be screened for dyslipidemia. The baseline lipid evaluation suggested is: total cholesterol, TG, HDL cholesterol, and LDL cholesterol. Most risk estimation systems and virtually all drug trials are based on total cholesterol and LDL cholesterol levels. Reduction of these parameters is associated with a statistically and clinically significant reduction in cardiovascular mortality and they thus remain the primary targets. Lifestyle interventions have an important long-term impact on health, and the long term effects of pharmacotherapy must be weighed against potential side effects.

Dietary factors linked to CVD risk reduction are mainly focused on the lipid levels, blood pressure, or glucose levels. Dietary recommendations are indicated in Table 9 for individuals with elevated total cholesterol and LDL cholesterol levels. Recently (2013) the EAS published a position paper on the impact of plant sterols on cholesterol homeostasis and cardiovascular risk, whereby they critically appraised evidence relevant to the benefit of functional foods with added plant sterols, as components of a healthy lifestyle to reduce LDL cholesterol levels and thereby lower cardiovascular risk. The EAS concluded that functional foods with plant sterols may be considered in patients with elevated cholesterol levels at intermediate and low global cardiovascular risk who do not qualify for pharmacotherapy; and as an adjunct for the high and very high risk patients receiving pharmacotherapy who do not reach LDL cholesterol targets it can be used as an adjunct.[20,48] Functional food containing phytosterols consumed in combination with statins is documented as being safe and well tolerated, and is shown to reduce LDL cholesterol by 5-10%.[9,70,71]

### 2.5.7. South African Lipid Guidelines

In 2000, a working group of the South African Medical Association and Lipid and Atherosclerosis Society of Southern Africa published a clinical guideline for the diagnosis, management and prevention of the common dyslipidemias in South Africa. The South African Lipid Guidelines are broadly based on the EAS guidelines on CVD prevention and it recommends immediate treatment of very high risk patients with established CVD, type 2 diabetes, genetic dyslipidemia and CKD to an aggressive LDL cholesterol target of <1.8 mmol/L. To reach this, an effective statin and combination therapy will be needed. Health resources are limited in South Africa, therefore therapy has to be prioritised to those at highest risk; this approach is emphasised in the European guidelines. Cardiovascular risk factors are particularly prevalent in the South African population and are set to increase because of increasing urbanisation. There is a clear relationship between urbanisation and the increase in cardiovascular risk factors, including an adverse effect on patients' lipid profiles. The prevalence of hypercholesterolemia is increased in the age groups 30 years and older (using the cut-off of 5 mmol/L), and the data suggests that more than 5.5 million patients carry a risk for a chronic

disease of lifestyle by virtue of their total cholesterol levels. Older African women who tend to have increased rates of obesity, are shown to be more at risk for hypercholesterolemia.[68,69,70]

The higher the absolute risk (using the Framingham risk score, as mentioned in 2.5.2), the greater the absolute benefit of lowering LDL cholesterol. Hypercholesterolemia is the most common and most significant, clinically, of all the dyslipidemias; and the classification thereof according to the EAS can be seen in Table 10. A full lipogram for these patients at higher risk is recommended. These guidelines recommend that optimum lipid levels and treatment goals will be met with intensive lifestyle intervention, and where this proves to be insufficient lipid-lowering drugs should be used. The lifestyle intervention can be seen in Table 9.[69,70,71]

**Table 10:** Classification of Hypercholesterolemia as used in South Africa[70]

| | Desirable lipid profile (mmol/L) | Target for ESRD (mmol/L) | Hypercholesterolemia | |
|---|---|---|---|---|
| | | | Moderate | Severe |
| Total cholesterol* | ≤ 5 | ≤ 5 | 5.0 - 7.5 | >7.5 |
| LDL cholesterol** | ≤ 3 | < 2.6 (<1.8 if diabetic) | 3.0 - 5.0 | >5.0 |
| HDL cholesterol | ≥ 1.2 | ≥ 1.2 | Variable | Variable |
| TG | ≤ 1.5 | ≤ 1.5 | <1.5 | <1.5 |

**For high risk patients (Total Framingham CVD risk of 15-30%) and very high risk patients (Total Framingham CVD risk of >30%) a total cholesterol of <4.5 mmol/L is recommended*
***For high risk patients the target LDL cholesterol should be <2.6 mmol/L, and very high risk patients the target LDL cholesterol should be <1.8 mmol/L (ESRD and ESRD patients with Diabetes respectively)*

In conclusion the guidelines stress that the management of hypercholesterolemia requires appropriate and aggressive lifestyle management for all patients. Lipid reducing drugs should be used in high risk patients in whom diet and exercise alone are deemed to be inadequate in terms of reducing LDL cholesterol levels.[9,69,70,71]

### 2.6. NUTRITIONAL STATUS ASSESSMENT

All stages of ESRD require careful nutritional status assessment, monitoring and dietary modification. Nutrition therapy differs based on the stage of ESRD and dialysis status. But it remains essential to enhance dialysis, maintain optimal nutritional status, and prevent complications.[2,26] It is important to screen all patients with ESRD for dyslipidemias, among other complications like protein energy malnutrition (PEM, caused by inadequate dietary intake or unmet nutritional requirements which are said to affect the level of GFR negatively) and treat them appropriately, as approximately 58% of these patients die from CVD.[5,6,15,16,17,21,22,27] The primary prevention of CVD involves the

assessment and monitoring of patients long term nutritional status with multiple risk factors at all ages by the dietician (NCEP, 2001).[2,26] Nutritional status should be assessed in all ESRD patients using standard techniques. Variables to be measured include anthropometric measurements such as weight and height (for BMI), and waist circumference; clinical assessment, various biochemical variables (lipogram, creatinine, etc.); and diet history.[15,16,17,21]

### 2.6.1. Anthropometric assessment

Anthropometrical measurements are valid clinically useful markers of a patient's nutrition status, particularly with regard to states of energy balance (depletion and excess). Body composition changes, especially muscle loss, occur during progressive renal failure.[15,16,17,21]

Whatever the mode of dialysis therapy, wasting and malnutrition (<25$^{th}$ percentile of ideal weight according to NHANES II) generally occur with increasing dialysis duration. Factors that contribute include chronic inflammation, inadequate food intake, restrictive diets, delayed gastric emptying, diarrhoea, the catabolic stress associated with frequent intercurrent illness, medication causing dyspepsia, suppressed oral intake secondary to peritoneal dialysate glucose load, inadequate dialysis, depression, altered sense of taste, and intradialytic nitrogen losses.[15,16,17,21,29,72] Worsening of PEM over time is also associated with a greater risk for cardiovascular death in renal patients.[22] If PEM is present, dietary restrictions are to be used judiciously, if at all, including for dyslipidemia.[72]

The condition of overweight and obesity are classified by the BMI. Body mass index (weight in kilograms/height$^2$ in metres) is frequently used as a surrogate measure of fatness in children and adults. Table 11 shows the classification of overweight and obesity developed by a NHLBI task force, along with the associated disease risk (such as CVD) with increasing BMI and waist circumference. Obesity usually coexists with CVD, glucose intolerance and diabetes, dyslipidemia, albuminuria, and hypertension.[2,7,26,72] Prospective studies that have reported follow-up data greater than two decades, such as the Framingham Heart Study, the Manitoba Study, and the Harvard School of Public Health Nurses Study, have documented that obesity is an independent predictor of clinical CHD; and as a whole it predisposes or is associated with numerous other cardiac complications (such as heart failure, and sudden death) through its impact on the cardiovascular system.[8,73,74,75,76] Gerber et al (2005) found that obesity is a known cause to decline in renal function. It potentiates atherosclerosis as it is the key factor leading to a pro-inflammatory and prothrombotic state. Adiposity is the principal nutrition-related influence found in atherogenic dyslipidemia. As a result a major goal is to attain and maintain an ideal body weight, as dyslipidemia is directly related to an increased BMI.[2,8,19,22,26] Studies have shown that intentional weight loss of 4.5-9 kg or 5-10% of usual body

weight can decrease proteinuria by 1.7 g (95% CI 0.7-2.6 g, P<0.05, with 1 kg weight loss proteinuria is reduced by 110 mg P<0.001) and albuminuria by 14 mg (95% CI 11-17 mg, P<0.05, with 1 kg weight loss albuminuria is reduced by 1.1 mg P=0.011) independent of reduction in blood pressure, improve atherogenic risk factors, such as LDL cholesterol, HDL cholesterol, TGs, high blood pressure, glucose tolerance, and C-reactive protein levels, even if an ideal BMI is not achieved.[2,5,8,26] Benefits of weight loss need to be individually assessed based on the patient's comorbid conditions and nutritional status. In patients receiving RRT, the focus should be placed on body composition rather than on weight loss; because interventions that improve overall fitness may improve survival and quality of life. Thus overall, one should aim for a healthy weight and abdominal circumference; and include physical activity each day to reduce metabolic demands on the kidney and as a result delay progression of ESRD.[5,22,72]

**Table 11:** Classification of overweight & obesity by percentage body fat, Body Mass Index, waist circumference, and associated disease risk

| | | Disease Risk* Relative to Normal Weight & Waist Circumference | |
|---|---|---|---|
| | BMI, | Men ≤ 102cm | Men >102cm |
| | $kg/m^2$ | Women ≤88cm | Women >88cm |
| Underweight | <18.5 | | |
| Normal | 18.5 - 24.9 | | |
| Overweight | 25.0 - 29.9 | Increased | High |
| Obesity, class | | | |
| I | 30.0 - 34.9 | High | Very High |
| II | 35.0 - 39.9 | Very High | Very High |
| III | ≥40 | Extremely High | Extremely High |
| **Disease risk for Type 2 Diabetes, Hypertension, & CVD* | | | |
| *From the Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults: The Evidence Report: National Institutes of Health* | | | |

Body mass index does not distinguish between fat-free and fat mass. Some patients may have a normal BMI, but their body fat may be preferentially distributed around the abdominal area which remains a strong predictor of mortality secondary to increased cardiovascular risk, and it may also incorrectly classify an extremely muscular individual as being overweight. It was recently suggested that the documented association between obesity, CVD, fasting insulin, insulin sensitivity, and blood pressure may be explained by phenomena related to the concomitant variation in the amount of abdominal fat, as estimated by waist circumference. Thus evaluation of the effects of excess weight for the prediction of cardiovascular events and mortality, should consider the distribution of body fat as well as the amount of adipose tissue in ESRD patients. [8,72,76,77] There is a significant interaction between TGs and waist circumference. Predictive value of TGs and cholesterol for survival and atherosclerotic complications in HD patients is critically dependent on waist circumference. Thus intervention studies in ESRD should specifically target patients with abdominal fat and

hyperlipidemia.[72,78] As a result obesity with a high waist circumference is especially important to correct in both men and women to improve atherosclerotic dyslipidemia and hypertension. This is because abdominal fat modifies the effect of lipids on atherosclerosis and as a result waist to hip ratio is a greater predictor of CVD than BMI alone.[8,72,76,77] This association remains significant after being adjusted for other risk factors, such as non-HDL and HDL cholesterol concentrations, hypertension, and smoking.[8,19] This measurement is not always relevant in all ESRD patients receiving RRT, namely PD patients where the presence of dialysate in the peritoneal cavity will skew the interpretation of these measurements. As a result BMI is the favoured anthropometric assessment tool to use (using dry body weight) in this patient subgroup to assess CHD risk status.

### 2.6.2. Biochemical assessment/ laboratory tests

In the presence of renal impairment, biochemical markers require more specific interpretation.[15,16,17,21]

The principle reason to evaluate dyslipidemias in patients with ESRD is to detect abnormalities that may be treated to reduce the incidence of atherogenic CVD. Therefore the K/DOQI guidelines on dyslipidemias in ESRD suggest that all patients should be evaluated more often than is recommended in the general population for dyslipidemias by completing a fasting lipid profile (lipogram) with total cholesterol, LDL (measured with the Friedewald equation which is considered reliable in dialysis patients) and HDL cholesterol, and TGs measured to identify those at risk and those who require treatment. Fasting measurements obtained by venopuncture should be taken prior to heparin use (influences lipoprotein metabolism), but, for practical reasons, peritoneal dialysis is not stopped prior to testing for a true fasting state.[4,15,16,17,21,22,27] Just as increased readings are associated with CVD and increased mortality in PD patients, decreased plasma cholesterol concentrations (<2 mmol/l) are predictive of increased mortality risk from stroke, cancer and other noncardiovascular diseases, as it is associated with chronic PEM and/or the presence of comorbid conditions, including inflammation.[5,15,16,17,21,22] The relationship between hypocholesterolemia and increased mortality is not observed in PD patients, possibly owing to increased glucose uptake and/or hypertriglyceridemia.[4]

### 2.6.3. Dietary Assessment

Comprehensive nutrition counselling should be offered to all patients with ESRD, given the high incidence of malnutrition and other nutritional abnormalities such as dyslipidemia. The diet needs to be individualised to accommodate each patients unique circumstances (palatability, cost, comorbid medical conditions, and cultural eating habits), for increased adherence. Skills to help them set goals

and resolve difficulties with lifestyle changes is also necessary.[6] Only if the patient is well nourished can dietary modifications for comorbid medical conditions, such as dyslipidemia, be safely undertaken. If the patient is malnourished and dyslipidemia is present, dietary modifications are used judiciously, if at all. Dietary management of ESRD patients with dyslipidemia is not specifically addressed in the KDOQI nutrition guidelines (Table 9), but rather extrapolated from the general population as indicated previously (TLC guidelines).[4] The TLC guidelines are said to reduce cholesterol by approximately 5%, which may seem low but it is related to poor compliance.[58] This effect may be enhanced by including a functional food like a sterol-enriched spread to be used as a spread and not for frying or cooking so as to better estimate the intake thereof.[25,55,58]

Patients with ESRD assume responsibility for their diets, and most long term patients know their diets very well having been instructed many times by dieticians at their dialysis units. Long term compliance with difficult diet regimens should be assessed on a regular basis by a dietitian.[2,26] The dietician can measure compliance by asking the patient to complete a three-day dietary record. This may be difficult especially with those patients who have low literacy levels. Assessment of food intake can also be achieved using a food frequency questionnaire or 24-hour food recall. Inadequate and low compliance can undermine the effectiveness of both pharmacological and therapeutic lifestyle regimens. The time taken to explain the condition and treatment can increase compliance, together with increased patient perception of the efficacy of treatment being given.[6]

### 2.7. TREATMENT FOR DYSLIPIDEMIA IN PATIENTS' RECEIVING RRT

Identifying dyslipidemia is done with a fasting lipogram which allows for a comprehensive assessment that includes measurement of total and LDL cholesterol, TGs and HDL cholesterol. Lifestyle modification with an emphasis on normalisation of body weight and cardioprotective dietary intake is recommended for effectively reducing total cholesterol and LDL cholesterol levels. Among patients with pre-existing CHD, large scale randomised trials have demonstrated that lowering LDL cholesterol concentration by 1 mmol/L for four to five years reduces the risk of coronary events and strokes by about 25%. Diet does not completely correct lipid abnormalities and very often, lipid-lowering medications are required in conjunction with diet.[6,27,33] The challenge is to implement programmes that effectively identify those at highest risk. This can be done by offering a maximal ratio of benefit to harm together with the most cost-effective interventions for ESRD patients that are at high risk for vascular disease.[5,6,33]

### 2.7.1. First and second line of therapy

Even patients with 'normal' cholesterol and pre-existing CHD benefit from treatment that reduces LDL cholesterol. The first step in selection of LDL lowering therapy is to assess a person's risk status. Risk assessment requires measurement of LDL cholesterol as part of lipoprotein analysis (Table 3) and identification of accompanying risk determinants (refer to section 2.5.2 NCEP ATP IV).[13] The therapeutic goal for lipids should be to achieve LDL cholesterol of 2.6 mmol/L and a fasting total cholesterol level of <5.6 mmol/L (Table 2).[6]

First-line therapy for most dialysis patients with dyslipidemia is dietary and lifestyle modification (Table 12). This is achieved by following the TLC guidelines mentioned previously which include diet (includes therapeutic agents like phytosterols), weight reduction, increased physical activity, abstinence from alcohol, smoking cessation (results in 50% decrease in CHD risk, and within 15 years the relative risk of CHD mortality approaches that of a lifetime non-smoker [AHA,2001]), and treatment of dyslipidemia if present.[2,6,25,26,29,80] If blood cholesterol levels are sufficiently low, the other dominant risk factors, including cigarette smoking, hypertension, and diabetes mellitus, constitute less of a threat.[25] The AHA recommends an 'adequate' trial (i.e. 6-12 months) of TLC before considering lipid-lowering medications (second-line therapies, Table 12) together with screening for risk factors, and providing education on disease, diet and medications. All of which prevents progression of atherosclerosis.[6,22,29]

**Table 12:** Treatment Recommendations for Dyslipidemia in Dialysis patients[4,27]

| Dyslipidemias (mmol/L) | Target (mmol/L) | Initial regimen | Treatment |
|---|---|---|---|
| [a]TG ≥ 5.6 | [a]TG < 5.6 | [b]TLC | [b]TLC + fibrates/niacin |
| [c]LDL ≥2.6-3.4 | [c]LDL < 2.6 | [b]TLC | [b]TLC + low dose statin |
| [c]LDL ≥3.4 | [c]LDL < 2.6 | [b]TLC + low dose statin | [b]TLC + max dose statin |
| [a]TG ≥ 2.3 & non-[d]HDL ≥3.4 | non-HDL < 3.4 | [b]TLC + low dose statin | [b]TLC + max dose statin |

***[a]TG Triglyceride; [b]TLC Therapeutic Lifestyle Change; [c]LDL Low Density Lipoprotein; [d]HDL High Density Lipoprotein; non-HDL cholesterol = Total cholesterol - HDL***

Although cholesterol-lowering medications could be prescribed to patients at high risk for developing high blood cholesterol, a long-term public health strategy that relies on providing medications to tens of millions of patients is not desirable for many reasons, including cost, inconvenience, and potential adverse effects. The five most common clinical situations in which drug

therapy is needed are 1) elevated LDL; 2) elevated non HDL cholesterol (total cholesterol – HDL) in patients with increased levels of TG despite attainment of LDL cholesterol goals; 3) decreased HDL cholesterol; 4) diabetic dyslipidemia; and 5) very high TGs. Effective drugs exist to improve lipid profiles, but no single drug is most appropriate under all circumstances.[6] The benefits of drug therapy should be weighed against the risk of complications (myopathy and rhabdomyolysis; muscle enzymes should be followed) that are increased in ESRD patients, as the kidneys are the main route of excretion (have a narrow therapeutic or toxic range).[4,5,27,61] Those at increased benefit include individuals with clinical ASCVD, primary elevations of LDL cholesterol ≥ 4.92 mmol/L, diabetics aged 40-75 years of age with LDL cholesterol between 1.81–4.9 mmol/L without clinical ASCVD, or without clinical ASCVD or diabetes with LDL cholesterol 1.81–4.92 mmol/L and estimated 10 year ASCVD risk ≥7.5%. Important possible exceptions for routine initiation (not for discontinuation if started prior to treatment or diagnosis) of statin treatment include individuals requiring maintenance HD or with class II - IV ischemic systolic heart failure (ACC/AHA expert panel made no recommendation regarding initiation/continuation of statin therapy in these two groups of patients). Although statin therapy did not reduce ASCVD events in these 2 groups, there was insufficient information on which to base recommendations for or against statin treatment keeping in mind potential for ASCVD risk reduction benefit, adverse effects, and drug-to-drug interactions, among other factors.

Characteristics predisposing individuals to statin adverse effects include, but are not limited to: multiple or serious comorbidities (impaired renal or hepatic function); history of previous statin intolerance or muscle disorders; unexplained ALT elevations >3 times ULN; patient characteristics or concomitant use of drugs affecting statin metabolism; and those ≥75 years of age.[5,17] Hence in these patients who would otherwise require high intensity statin treatment, moderate intensity statin therapy should be used at the clinicians discretion. The ACC/AHA expert panel did not find ASCVD outcomes for plant sterols, sterol esters, stanols, or stanol esters partly because of lack of trials available for evidence review during this timeframe. Thus no recommendations were made regarding its use.[18,19] Patients on lipid-lowering treatment often do not reach the goal for LDL-cholesterol concentrations as set by the NCEP, thus combination treatments that act by different mechanisms may be more appropriate. As a result diet and therapeutic dietary agents such as spreads enriched with plant sterol or stanol esters can be useful adjuncts to drug therapy (result in a further 10% decrease in LDL cholesterol levels).[80,81]

The classes of drugs that can be used to treat these lipid abnormalities in this population group include: (1) bile acid sequestrants; (2) nicotinic acid; (3) ezitimibe; (4) fibrates (contraindicated in ESRD); and statins can either be used singly or in combination (Table 13).[13,29,31,33] Statins (HMG-A reductase inhibitors, decrease cholesterol production and upregulates LDL receptors in the liver, figure 3) are the drug of choice to lower LDL cholesterol and have the most favourable effect on reducing cardiac mortality in patients with moderate ESRD (GFR of 30 to 59.9 ml/min/1.73m$^2$), provided there is no evidence of acute or chronic liver disease. Statins also reduce proteinuria and slow the decline in renal function (this effect was more significant in patients with proteinuria).[4,6,15,16,17,21,22,27,81] The recommended use of statins are based on extrapolation of beneficial results in the general population (as with dietary agents like sterols and stanols on reducing LDL cholesterol and TG, and increasing HDL cholesterol, shown in Table 13), as confirmatory randomised control trials in the dialysis population were on-going. The Study of Heart and Renal Protection (SHARP, the largest RCT in patients with CKD to date) one of the few studies including CKD patients (adults aged >40 years of age), of which 33% were receiving dialysis (peritoneal or hemodialysis), ezitimibe 10 mg was co-administered with simvastatin 20 mg and compared to placebo. The study found that LDL cholesterol was reduced by 33% in those not receiving dialysis, and by 23% in those receiving dialysis; CVD events were not reduced in those with CVD nor in those receiving hemodialysis; the statin modestly increased the risk of muscle symptoms requiring discontinuation of treatment (1.1% versus 0.6% with p=0.02); and it did not increase the risk for elevated hepatic transaminases, cancer, haemorrhagic stroke, or non-cardiovascular mortality. The lipid-lowering strategy resulted in a 17% reduction in atherosclerotic events, and was considered effective and safe for this population group. This being said, several other large scale five year trials (4D, AURORA, including SHARP) showed statins to be safe and able to reduce CHD morbidity and mortality by approximately 30%.[5,17,81]

**Table 13:** Effects of antihyperlipidemic agents on lipid profile of adults[13]

| **Reduction of** | | **Increase of** | **Antihyperlipidemic agent** |
|---|---|---|---|
| **[a]LDL** | **[b]TG** | **[c]HDL** | |
| 18-55% | 7-30% | 5-15% | Statin |
| 15-30% | no change | 3-5% | Bile acid sequestrant |
| 5-25% | 20-50% | 15-35% | Nicotinic acid |
| 5-20% | 20-50% | 10-20% | Fibrates |
| 9-20% | no change | no change | Phytosterols |

*[a]LDL Low Density Lipoprotein; [b]TG Triglyceride; [c]HDL High Density Lipoprotein*

Fixed doses of higher- and moderate-intensity statin therapy did not reduce atherosclerotic CVD events in those with New York Heart Association (NYHA) class II-IV or receiving maintenance hemodialysis. But there was insufficient information on which to base recommendations for or against statin therapy for these two groups. More studies with dose-adjusted statin treatment to achieve pre-specified LDL cholesterol goals in this population group are needed to investigate how to avoid toxicity, and the age of the patient should be considered. The potential for atherosclerotic CVD risk reduction benefit, adverse effects, and drug-to-drug interactions along with other cautions and contraindications to statin therapy and choice of statin dose must also be considered by the treating clinician. The ACC/AHA found extensive and consistent evidence supporting the use of statins for individuals at increased atherosclerotic CVD risk who are most likely to experience a net benefit in terms of the potential for atherosclerotic CVD (individuals with clinical atherosclerotic CVD, primary increase of LDL cholesterol ≥ 4.9 mmol/L, diabetics aged 40-75 years with LDL cholesterol 1.8-4.89 mmol/L and without clinical atherosclerotic CVD, or without clinical atherosclerotic CVD or diabetes with LDL cholesterol 1.8-4.89 mmol/L and estimated 10 year atherosclerotic CVD risk ≥7.5%) risk reduction and the potential for adverse effects.[5,17]

The 4D and AURORA meta-analysis, mentioned above, used statin monotherapy, which reduces endogenous cholesterol synthesis via inhibition of HMG-CoA reductase. The SHARP study used dual therapy (statin and ezitimibe), that reduced both endogenous cholesterol synthesis and exogenous cholesterol absorption via two separate cholesterol homeostasis mechanisms. All these therapies showed promising results in CKD patients. Assessing these studies led to the investigation of the individual response to dietary cholesterol intake and the current treatment modalities used to try to reduce cholesterol levels in hypercholesterolemic individuals, such as CKD patients receiving HD, and classifying them as either hypo or hyper-responders. Hyper-responders have low basal rates of cholesterol synthesis and increased serum cholesterol levels secondary to exaggerated response to dietary cholesterol intake. Hypo-responders have higher rates of basal cholesterol synthesis and less efficient absorption of dietary cholesterol. This subgroup of individuals tended to have lower serum cholesterol levels despite having increased rates of synthesis; as a result they responded well to statin therapy. The study by Rogacev et al investigated whether ESRD patients receiving HD, who are at increased risk for ASCVD events not solely related to increased LDL cholesterol, fall into the aforementioned categories. Using previously validated methods of measuring this such as lathesterol (marker of cholesterol synthesis) and cholestanol (marker of cholesterol absorption) they concluded that the patients were hyper-responders. The mechanisms that underlie this shift in cholesterol absorption in this patient subgroup are not yet fully understood but may be due to

reduced hepatic clearance of transport proteins (chylomicrons and VLDL) commonly seen in CKD, or may be due to a reduction in endogenous cholesterol synthesis and as a result a consecutive increase in cholesterol absorption occurs to maintain homeostasis. There are limitations to the study which included a small sample size, and it may be possible that the validated methods of measuring synthesis and absorption from the general public may not be validated in HD patients. Nevertheless, the current study gives insight into improving our understanding of differing results of cholesterol-lowering trials in patients with CKD and may affect future clinical decision-making processes. Further research with a larger cohort is necessary to validate these findings, but this reaffirms the need for these patients' diets to conform to the KDOQI and KDIGO guidelines including TLC recommendations regarding nutritional support.[10,11,12]

When pharmacotherapy is combined with plant sterols, enhanced effects are evident. Plant sterols lower the bioavailability of intestinal cholesterol for entry into circulation. Statins directly decrease intracellular levels of cholesterol and its precursors, enhances the catabolism of ApoB-containing lipoproteins (mainly LDL) via upregulation of hepatic LDL receptors, and reduces de novo hepatic (and potentially intestinal) lipoprotein production. Thus plant sterols may exert an additive effect when combined with a statin (10-15% reduction verse doubling the statin dose and getting a 6% reduction in LDL cholesterol). Ezitimibe inhibits intestinal cholesterol absorption (16% reduction in LDL cholesterol levels) by blocking the NPC1L1 transporter, whilst plant sterols displace cholesterol from intestinal micelles which cause the cholesterol to enter via the NPC1L1 gate; thus a significant incremental reduction of a further 7% occurs in intestinal cholesterol absorption.[10,11,12,20,36]

## 2.8. CONCLUSION

Cardiovascular disease is by far the leading cause of morbidity and mortality in dialysis patients, accounting for almost 40% of hospitalisations and almost 50% of deaths, and, after stratification for age, race and gender, the cardiovascular mortality rate those with ESRD receiving dialysis, are highly prone to CVD for a number of reasons. In order to prevent or at least delay the development of cardiac abnormalities, it is vitally important to understand the determinants of CVD and to prepare interventions aimed at improving the management of ESRD patients.[26] A multidisciplinary, collaborative approach is essential to help patients achieve the target cholesterol, LDL, HDL and TG levels necessary to reduce cardiovascular risk.[6]

Ideal blood lipid levels can be accomplished only by adherence to lifestyle and pharmacological regimens. A collaborative approach between nursing, nutrition, and medicine facets will provide improved patient compliance, greater ability to reach lipid goals, and greater safety.

A reduction in LDL cholesterol of approximately 10%, is said to reduce the incidence of CHD by 10-20%. Although no direct evidence is available yet for the ability of phytosterols to lower CHD incidence, the well-documented cholesterol-lowering effect of phytosterols is the basis for recommendations to include phytosterol in strategies to lower LDL cholesterol concentrations.[41] Lipid-lowering drugs are costly, and are frequently associated with side effects and compliance issues. Medical therapies are complex and require patient education, systematic medical follow up, and on-going management.[6] The percentage of LDL cholesterol reduction may not only indicate adherence, but may also reflect biological variability in the response to lifestyle, as well as the use of plant sterols and drug therapy (statins). This acknowledges the fact that some individuals may have a less than an average anticipated response, and that adherence to statin and lifestyle therapy, as well as evaluation and treatment of secondary causes that may increase LDL cholesterol, needs to be continually evaluated.[17]

Dyslipidemia occurs particularly frequently in ESRD patients, but the benefit of lipid-lowering treatment still needs to be proved.[26] There is an urgent need to confirm guideline statements from studies in the general population in patients with ESRD. There are reasonable doubts as to whether RCTs from the general population regarding the use of plant sterols and stanols can be extrapolated to all patients with ESRD, as most trials in the general population have excluded patients with elevated serum creatinine and Stage 5 ESRD.[4]

# CHAPTER 3: METHODS

## 3.1. STUDY METHODOLOGY

### 3.1.1. Study design

The study was conducted from November 2014 to May 2015 and was a randomised, double-blind, prospective, cross-over, controlled trial, in which 89 chronic dialysis patients signed the informed consent, but only 73 completed the trial, and this was later controlled for those who consumed the specified 25g per day further reducing the number of participants evaluated to 49 (n=27 and n=22 for PD and HD participants' respectively). At the baseline, the participants were randomly assigned to one of the two groups, namely the group receiving the control margarine (Floro extra light) and the other group receiving the test margarine (Floro proactive) for eight weeks. The dietician, randomly selected the two groups on the basis of HD or PD treatment modality being received for logistical purposes. Clinical and laboratory assessments were performed at baseline, after eight weeks of trial, after four weeks of washout, and again after another eight weeks of trial (when participants changed from what they received previously). The participants and the researcher/dietician were blinded to which group was receiving the control or the test margarine.

### 3.1.2. Sampling

A statistically representative sample (P 0.05) of 89 participants in total, 44 from HD and 45 from PD clinics at CMJAH, was included in the study. Prof Nel, the allocated statistician at Stellenbosch University, had determined that a statistically representative sample size would be 88 (P 0.05, Power RMSSE 50%), using a 1-Way ANOVA sample size calculation. Stratified random sampling was used to obtain two groups with comparable variation of characteristics of interest between two strata, namely those receiving HD and those receiving PD. Of which 49 of the 73 participants were controlled for as they consumed the specified 25g per day (n=27 and n=22 for PD and HD participants' respectively). Using the 1-Way ANOVA sample size calculation the effect size was 64% and 71% (RMSSE, P 0.05) for PD and HD groups respectively.

### 3.1.3. Inclusion criteria

Those included in the study were patients who consented to participate, who were older than 21 one (adults) years of age, and that were receiving either peritoneal or hemodialysis at CMJAH. Patients both receiving and not yet receiving statins were also included in the study.

### 3.1.4. Exclusion criteria

Patients that were excluded from the study were those who did not give consent to participate, or didn't meet the inclusion criteria.

## 3.2. METHODS OF DATA COLLECTION

Information was obtained from the participants involved in the study in the HD and PD clinics at CMJAH. All measurements were taken by the same registered dietician throughout the course of the study. Data were collected from November 2014 to June 2015 at CMJAH using a standardised data collection form (Addendum A).

### 3.2.1. Blinding and randomisation

The researcher was blinded as to which coded tubs (A or B) contained the placebo (Floro extra light, not fortified with plant sterols) or the margarine enriched with plant sterols and stanols (Floro proactive, fortified with plant sterols). The placebo and test margarine was randomly placed into unlabelled clear containers at the start of the study, which were later labelled 'Tub A' and 'Tub B' by a volunteer not involved in or affiliated to the study. The volunteer wrote which margarines were placed in the aforementioned tubs on a paper and sealed it in an envelope. This individual later handed over the sealed letter describing the portioning done at the start of the research which, was later opened (at completion of data collection for the study). The letter indicated which group received which margarine. The HD and PD participants who had given informed consent and met the inclusion criteria were selected using stratified random sampling in order to obtain comparable variation of characteristics of interest between the two strata. They received 'Tub A/B' initially, which may have contained the placebo or test margarine, followed by a washout period when nothing was given, and finally they received the opposite 'Tub A/B' to that which they had received at the start of the study (this constituted the cross-over). By blinding the participants and the researcher to what the participants were receiving, possible bias and misuse of the margarines (double-blinded study) were avoided.

### 3.2.2. Intervention

A prospective, cross-over, randomised control trial, was conducted, wherein a statistically representative sample (P 0.05) participated from both HD (n=44) and PD (n=45) patient groups attending CMJAH. Initial total cholesterol, LDL cholesterol, HDL cholesterol and TG levels were compared prior to and post intervention. The HD and PD patients were selected using stratified random sampling. Both groups were counselled about the aims of the study, as it was thought that this would enhance compliance within the study keeping in mind moral, legal and regulatory needs for full disclosure to the participants.

All participants (HD and PD) were randomly given either the placebo or the test margarine initially for eight weeks. During this time 25 g/d were to be consumed by each participant (a measuring spoon was given to each patient to help to measure off 25 g). The patients then underwent a washout period, when they received neither the placebo nor the test margarine for four weeks. After the washout period those participants who initially received 'Tub A' later received 'Tub B' in the last eight weeks of the study (the cross-over occurred in the second part of the trial). All the spreads used in the study were indistinguishable in taste and appearance. All containers were to be returned to the investigator after each of the eight weeks so that compliance could be determined (where they were weighed and recorded on the information sheet). The participants were given standardised portioning spoons to aid with correctly measuring 25 g of margarine per day, which was to be used throughout the study. It was thought that this would improve accuracy of the diet and promote compliance. The serum lipid level of each participant was recorded to obtain a baseline prior to initiating the study. After eight weeks of consuming the test or placebo margarine (serum lipid levels were recorded); a washout period ensued (serum lipid levels were recorded). After the final eight weeks of the study serum lipid levels were again recorded. All participants had been previously counselled using TLC guidelines within the NKF-K/DOQI and KDIGO guidelines by the researcher prior to the start of the study as they are all long term patients who upon diagnosis receive dietary counselling. Due to Floro proactive margarine being expensive, patients in the government setting were not told to use it prior to the start of the study, and post completion of their baseline 24 hour recall, none of them indicated that they had ever used the sterol enriched margarine prior to the start of the study. Their dietary intake was assessed using a 24-hour recall (HD participants dietary recall was obtained for non-dialysis days), completed at the start of the study and after each of the eight week intervals. This was done, as it may be seen as a possible confounding variable to the results obtained. A framework highlighting how data collection occurred can be seen in figure 6.

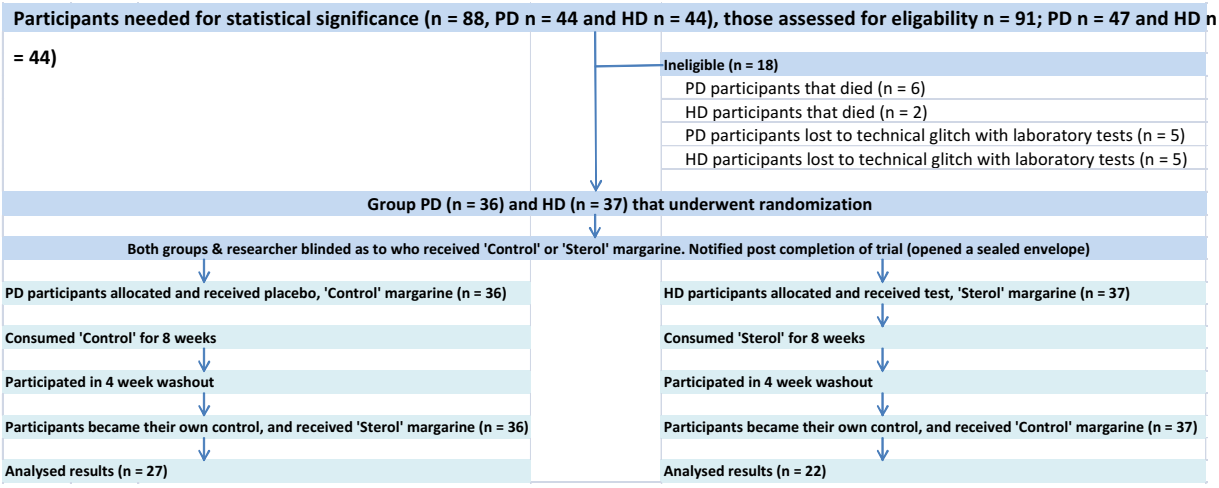



**Figure 6:** CONSORT illustrating the sequence of events in the present study.

### 3.2.3. Demographic information

Variables, for example, age and gender were obtained using the data collection form in Addendum A. The form was completed at the start of the study by the registered dietician once the participants had signed the informed consent form (Addendum B).

Etiology of CKD, duration and type of RRT being received, type of PD solution being received and number and type of exchanges of PD solution per day (I asked whether or not their dialysate changed when the 24hour recall was obtained from the respective participants during the course of the trial) as well as traditional risk factors were determined. Traditional risk factors for ESRD related to the increased prevalence of CVD such as family history of CVD, existence of comorbid conditions, smoking and level of physical activity were noted on the data collection form. 'Moderately active' was interpreted as the participant being active at work, and 'active' was seen as the participant being active three times per week for 30-45 min at a time.

## 3.3. NUTRITIONAL STATUS

### 3.3.1. Anthropometric assessment

Standard techniques were used for all the participants in order to determine their nutritional status. For the purpose of the study, the anthropometric assessment included weight and height, percentage usual body weight, percentage standard body weight (using the NHANES II tables), body mass index (BMI) and waist circumference (80-88 cm for females and 94-102 cm for men, where

applicable).[3,42] The patients height was measured (to the nearest 0.1 cm) once off and captured on the data collection form by the registered dietician at the start of the study once the participants had signed the informed consent form, using a stadiometer attached to the SECA scale. All participants were required to remove their shoes, to stand up straight with feet together, with buttocks, shoulder blades and head against the measuring device and to look straight ahead. No estimations of height were necessary as all participants were able to stand. The participants were asked for their usual dry weight so as to determine whether they had recently experienced weight loss or gain (current weight as a percentage of their usual weight), and the significance thereof was determined using the formula below:

Percentage of weight loss = (usual weight – amount of weight lost) / usual weight x 100

To determine the standard body weight, a frame size for each of the participants was necessary. The right wrist circumference was measured in cm with a tape measure, whereby the arm was flexed at the elbow with the palm facing upward and the hand muscles relaxed. The measuring tape was placed around the wrist crease between the styloid processes of the radius and ulna and bones of the hand (above the wrist bone). The measurement thereof was interpreted using table 14.

**Table 14:** Determining frame size from the ratio of body height to the circumference of the right wrist

| Frame size | r Value | |
|---|---|---|
| | Male | Female |
| Small | r > 10.4 | r > 11.0 |
| Medium | r = 9.6 - 10.4 | r = 10.1 - 11.0 |
| Large | r < 9.6 | r < 10.1 |

***Adapted from Grant JP, Custer PB, Thurlow J. 1981. Current techniques of nutritional assessment. Surgical Clinics of North America 61:437-463***

Dry weight was recorded to the nearest 0.1 kg using the same calibrated SECA scale attached to the stadiometer (calibrated before beginning to weigh the participants with an item with a known weight every four weeks for the duration of the study). Dry weight for HD patients corresponded to the weight obtained post-dialysis and in PD patients that excluding the dialysate, both based on clinical judgement whether the patient still presented with clinical edema. If the latter was present adjusted edema-free body weight was used as shown below (standard body weight obtained through the NHANES II in Addendum D):

Adjusted edema free weight = dry weight + (standard body weight – dry weight) x 0.25

Percentage of standard body weight could then be calculated where necessary (% standard body weight = (actual weight / standard body weight) x 100) for later use when calculating whether nutritional requirements were adequately being met, and their nutritional status. Both the dry

weight and the height were used to calculate body mass index (BMI=weight/height$^2$) in order to indicate under- or over-nutrition (placing the individual at increased risk for comorbid conditions), as BMI is considered an independent measure of body fat for adults.

Waist circumference indicates increased risk for diabetes, CAD and hypertension as it is used to assess central fat distribution and degree of abdominal obesity. The standard technique used to measure waist circumference (to the nearest 0.1 cm) was where a non-stretchable tape measure was positioned horizontally, parallel to the floor, around the smallest area around the waist, below the rib cage and above the iliac crest (corresponds to the maximal abdominal diameter). All measurements were repeated three times, and the median of the readings was used in the assessment. This measurement was not done with PD participants as it would be inaccurate with the dialysate being in the peritoneum, and logistically all the PD clinic participants could not dialyse in the clinic on the respective measurement days in order to obtain this measurement. Hence, waist circumference was only measured in HD participants. Repeated weight and waist circumference measurements were taken at the start of the study (at baseline) and after each arm of the trial until the completion of the study, each time noting measurements on the data collection form (Addendum A). All measurements were taken by the same registered dietician.

### 3.3.2. Biochemical assessment

Plasma creatinine and lipid profile were analysed to determine the influence of plant sterols on the reduction of CVD risk.

In the presence of renal impairment, biochemical markers require more specific interpretation. The biochemical markers in this study included a lipid profile which was measured at baseline and twice thereafter after the first eight week intervention period, after the washout period, and after the final eight weeks of intervention at the participants monthly clinic visits. The lipograms were charted on the data collection form (Addendum A), to be used to determine the influence of plant sterols on the reduction of CVD risk. The NHLS at University of the Witwatersrand kindly offered discounted rates for lipogram tests that were used in this study to analyse total cholesterol, triglycerides, LDL and HDL cholesterol levels. The NHLS made use of clinical diagnostic laboratory methods, which were evaluated for conformance with NCEP guidelines. Hemodialysis participants had lipid profiles measured before dialysis and prior to heparin use. Measurements were performed by the respective renal nurses within the unit, at the same location (in the respective clinics) and approximately at the same time of the day (all participants had their time slot allocated, be it monthly for PD or weekly for HD) to enhance accuracy of the readings obtained. The experimental period of eight weeks seemed

relatively short, but there is ample evidence that lipid and lipoprotein responses to dietary changes in fat intake are rapid (three to four weeks, according to Durrington et al, 1977).[31] These analyses were used to determine the influence of plant sterols on improving lipid profiles in ESRD.

### 3.4. NUTRITION INTAKE AND COMPLIANCE WITH GUIDELINES

The quantity of plant sterols used per day, as well as a diet history, was assessed to monitor compliance according to what is considered necessary by the K/DOQI and TLC guidelines. There are a variety of methods that can be used by a dietician to determine long term compliance with difficult diet regimens like that of the renal diet (three day food record, food frequency questionnaire, or 24-hour recall).[3] The 24-hour recall was selected for this study because of poor literacy levels of the participants and to make quick access to dietary intake information possible (Addendum A). This was obtained by the registered dietician at baseline and after each eight week trial period, when she recorded a typical day's intake noting the participants' frequency of meals consumed (main meals and snacks), the description of the food or beverage consumed, and the methods used to prepare the food. Dietary assessment was done on non-dialysis days with HD participants.

All dietary assessments obtained were converted into nutrients namely: 1) total energy (energy obtained from dialysate was included here and under the carbohydrates assessed for the PD group); 2) percentage coming from carbohydrates; 3) percentage coming from protein together with the grams per kilogram ideal body weight; and 4) percentage coming from total fat, SF, cholesterol, MUFA and PUFA) intakes using the FoodFinder version III (developed by Medical Research Council of South Africa) and evaluated against the intake recommended earlier by the dietician according to the K/DOQI and TLC guidelines. Participants were asked not to make alterations to their habitual diets, levels of physical activity, smoking habits or use of alcohol during the course of the study. The tubs were returned at the end of every eight week period where they were weighed and their weights were recorded by the registered dietician to estimate compliance.

### 3.5. EFFECT OF PLANT STEROLS

All participants were asked whether lipid-lowering medication was being used, for how long, and at what dose. This was also charted on the data collection form (Addendum A). This would later be used to determine whether the plant sterols used had an additional effect on the participants' lipid results.

## 3.6. ANALYSIS OF DATA

### 3.6.1. Demographic data

Demographic information regarding the potency of effects obtained according to age and gender, etiology of CKD, duration and type of RRT utilized, type of PD solution being received and number of exchanges per day as well as traditional risk factors were assessed. The influence of these data on results obtained using plant sterols and stanols in the participants typical diet, and their influence on the participants' baseline lipid profiles were all noted as possible confounding variables to the efficacy of the plant sterols being utilised by the participants during the trial.

The traditional risk factors assessed that correlated with an abnormal lipid profile included older age, gender (males), presence of comorbid conditions (etiology of CKD [diabetes mellitus, hypertension, and left ventricular hypertrophy/systolic dysfunction]), smoking, dyslipidemia, physical inactivity and family history of CVD.

## 3.7. NUTRITIONAL STATUS

### 3.7.1. Anthropometric data

Anthropometry was assessed in terms of unplanned/unintentional weight loss of greater than 5% in one month or 7.5% loss in three months or 10% loss in six months.[82] This was considered significant.[82] Where the use of the adjusted edema-free body weight is necessary, it may be applied effectively for nutritional assessment and nutritional prescription when it is between 95 and 115% of the standard body weight (using the NHANES II tables). Edema-free body weight is used when assessing the participants' nutritional status and nutritional adequacy of their diet. Intentional progressive weight loss in those who are overweight or obese is noted in the literature to help reduce total cholesterol and LDL cholesterol levels. According to the World Health Organisation a BMI of less than 16 kg/m$^2$ was considered as Grade 3 (severe thinness), 16-16.99 kg/m$^2$ as Grade 2 (modest thinness), 17-18.48 kg/m$^2$ as Grade 1 (mild thinness), 18.5-24.9 kg/m$^2$ as normal weight, 25-29.9 kg/m$^2$ as overweight, 30-34.9 kg/m$^2$ as obese class I, 35-39.9 kg/m$^2$ as obese class II and >40 kg/m$^2$ as obese class III. The Malnutrition Advisory Group suggests that BMI of less than 18.5 kg/m$^2$ to be indicative of probable chronic protein energy under nutrition, 18.5-20 kg/m$^2$ possible chronic protein energy under nutrition, and >20 kg/m$^2$ unlikely to be chronic protein energy undernutrition. Body mass index of maintenance dialysis patients should be maintained in the upper 50$^{th}$ percentile (for women and men at least approximately 23.6 and 24 kg/m$^2$, or according to KDIGO guidelines 20-

25 kg/m$^2$ is ideal). A waist circumference greater than 102 cm for men, and 88 cm for women places the individual at increased risk for comorbid conditions, as well as with an increased BMI.

### 3.7.2. Biochemical data

The minimum serum total cholesterol is 2 mmol/l, and, if lower than this, it is associated with chronic protein energy deficits and/or the presence of comorbid conditions, including inflammation Will add the ref mentioned above (Liu). The relationship between serum total cholesterol and outcome is J-shaped with increasing risk of mortality as serum cholesterol falls below this minimum level.

### 3.7.3. Nutritional intake and compliance with guidelines

The dietary assessment obtained using The FoodFinder results was assessed according to K/DOQI and TLC guidelines as demonstrated in Tables 14 and 15 (Addendum D). The minimum goal for dietary protein intake in chronic ESRD patients receiving either PD or HD should be at least 1.1 g/kg ideal body weight, together with sufficient energy intake of 30-40 kcal/kg for an optimal metabolic balance (neutral or positive nitrogen balance). Both LDL cholesterol and total cholesterol are highly correlated, and diets that are high in saturated fat, trans fat and cholesterol are associated with an increase in these markers. By isocalorically substituting these fats with MUFA and PUFA, and including more soluble fibre and possibly including 2-3 g (25 g/d) plant sterols these levels may be reduced.

### 3.7.4. Statistical procedures

The analysis was performed with the assistance of Professor Nel, the allocated statistician at Stellenbosch University. MS Excel was used to capture the data and STATISTICA version 9 (StatSoft Inc. (2009) STATISTICA (data analysis software system) was used to analyse the data. Summary statistics were used to describe the variables. Distributions of variables are presented with histograms and/or frequency tables. Medians or means were used as the measures of central location for ordinal and continuous responses and standard deviations and quartiles as indicators of spread. Relationships between two continuous variables were analysed with regression analysis and the strength of the relationship measured with Pearson correlation, or with Spearman correlation if the continuous variables were not normally distributed. If one continuous response variable was to be related to several other continuous input variables, multiple regression analysis was used and the strength of the relationship measured with multiple correlation. The relationships between continuous response variables and nominal input variables (like different diets) were analysed using

appropriate analysis of variance (ANOVA) and appropriate repeated measures analysis of variance (RMANOVA) when responses were measured at specific time intervals. To account for possible confounding variables these variables could be included as covariates in appropriate analysis of covariance (ANACOVA). When ordinal response variables were compared with a nominal input variable, non-parametric ANOVA methods were used. For completely randomised designs the Mann-Whitney test or the Kruskal-Wallis test was used and for repeated measures designs the Wilcoxon- or Friedman tests were used. The relation between nominal variables was be investigated with contingency tables and appropriate chi-square tests for example the likelihood ratio chi-square test or the McNemar test. A p-value of $p < 0.05$ represented statistical significance in hypothesis testing and 95% confidence intervals were used to describe the estimation of unknown parameters.

### 3.8. ETHICAL AND LEGAL ASPECTS

- ✓ Ethics approval

  The study was submitted and given ethics approval from the Human Research Committee (HREC) at WITS University and the HREC of the Faculty of Medicine and Health Sciences of Stellenbosch University prior to the commencement of the study, with clearance certificate numbers M130765 and S12/11/291 respectively. The approval of the Medicines Control Council approval was not necessary as the margarine enriched with plant sterols and stanols was not intended to treat or cure patients, but is rather was seen as part of their dietary intake. Margarine is considered a foodstuff.

- ✓ Written informed consent

  Participants were given explanation of the important aspects of the study in terms of why it was being done, so that they could make an informed decision as to whether or not they intended participating in it. If the participants agreed to participate, they were provided with the placebo and test margarine for the duration of the study (and were not expected to purchase it themselves). A consent form that was culturally and linguistically sensitive was completed by all participants (Addendum B) and could be supplied in three different languages (English, Afrikaans, and Zulu), which are the main languages spoken by the population being investigated. The English consent form was approved by the HREC. Patients who did not sign the consent form were excluded from the study. Participants were made aware, as indicated on the form, that they could withdraw from the study at any time, if they wished to do so.

- ✓ Anonymity and confidentiality

  Information obtained was treated as confidential. The dietician was the only person who knew the specifics of each participant. To ensure anonymity participants were assigned numbers (names were kept confidential). While all information that was collected and a summary of the findings are presented in the final write up of the study, the anonymity of all participants has been maintained, and this information has remained confidential. This procedure was outlined in the informed consent forms and prospective participants were made aware of this before signing.

- ✓ Incentive to participate

  Data were collected at routine check-ups with no additional charges incurred by the participants.

- ✓ Risk/Benefit ratio

  The benefits of the study are that participants may experience overall improved nutritional status with the provision of the margarines secondary to increased caloric intake that may not have been possible previously owing to lack of money. Another benefit is the increased interaction with the dietician, to ascertain whether or not participants are meeting their nutritional requirements.

  The risk that the participant may experience is the increased number of blood tests to be undergone (lipid profile). Additional discomfort caused by drawing blood samples can be incurred, resulting in slight bruising or redness, and some participants may feel that the procedure is slightly painful. This will be minimised by using correct blood sampling techniques by trained nursing staff within the respective RRT units throughout the study.

- ✓ Conflict of interest

  The study was funded by a clinical research grant awarded by the International Society of Nephrology (ISN). Because funding came from outside sources that have no relationship with the products being used, there was no conflict of interest. Unilever, the manufacturer for Floro, was aware that the study was done using its products, but had no involvement in the study (products were purchased using external ISN grant money).

# CHAPTER 4: RESULTS

## 4.1. DEMOGRAPHIC INFORMATION

A total of 91 individuals agreed to participate in the study, of which 47 were from PD and 44 from HD. Not all of their results were included in the analysis, the reason being that either they died during the course of the study, or their laboratory tests were not available owing to technical problems. As a result, a total of 73 participants completed the trial (36 PD and 37 HD), this was controlled for those who consumed the specified 25g per day further reducing the number of participants evaluated to 49 (n=27 and n=22 for PD and HD participants' respectively). Complete data sets were obtained for all variables (demographics, information pertaining to the cause of disease, presence of comorbidities, form of treatment received and number of years participants received it, and level of physical activity shown in Table 15). The study sample consisted predominantly of middle-aged to older black individuals with a low-income socioeconomic status, 47% of whom were male in the PD group and 51% were male in the HD group – thus comparable in terms of gender distribution. The mean age of study participants was 39 years with ±10.5 years for PD and 41 years with ±12.2 years for HD, and the mean duration of treatment was four years for PD (range 1–10 years) and six years for HD (range 1–16 years). The major cause of CKD was hypertension: 78% of PD patients (71% with a family history) and 76% of HD patients (76% with a family history). For the rest the condition was attributable to diabetes, HIV nephropathy and other reasons (in descending order). A high majority of both the PD (72%) and HD (73%) group of participants indicated that they were moderately active, with only 11% and 19%, respectively, indicating that they were not active at all.

**Table 15:** Study and participant characteristics from clinical plant sterol intervention

| Variable | Measurement | PD (n) | HD (n) |
|---|---|---|---|
| **Age** | N | 36 | 37 |
| | Mean | 39 | 41 |
| | Minimum | 20 | 20 |
| | Maximum | 63 | 58 |
| | Std Dev | 10.5 | 12.2 |
| **Duration of treatment (years)** | N | 36 | 37 |
| | Mean | 4 | 6 |
| | Minimum | 1 | 1 |
| | Maximum | 10 | 16 |
| **Gender** | Male | 17 | 19 |
| | Female | 19 | 18 |
| **Race** | Black | 32 | 33 |
| | White | 1 | 1 |
| | Indian | 2 | 0 |
| | Coloured | 1 | 3 |
| **Cause of CKD** | HPT | 28 | 28 |
| | DM | 5 | 1 |
| | GN | 2 | 2 |
| | NS | 1 | 6 |
| **Family history CVD** | Yes | 20 | 21 |
| | No | 16 | 16 |
| **Level of activity** | None | 4 | 7 |
| | Moderate | 26 | 27 |
| | Active | 6 | 3 |
| **Use of statins** | 10mg | 2 | 1 |
| | 20mg | 11 | 4 |
| | 40mg | 2 | 1 |

## 4.2. NUTRITIONAL STATUS

### 4.2.1. Anthropometric status

Anthropometrical results at baseline are outlined in Table 16. The mean weight of the study participants was 66.7 kg for PD and 63.2 kg for HD participants. Female participants' mean BMI was 24.8 kg/m$^2$ (18.3–32.4 kg/m$^2$) and 22.6 kg/m$^2$ (16.8–38.6 kg/m$^2$) for PD and HD respectively; and the male participants mean BMI was 23.1 kg/m$^2$ (17.4–30 kg/m$^2$) and 23.4 kg/m$^2$ (14.2–33.4 kg/m$^2$) for PD and HD respectively. Overall average BMI for PD participants was 24.09±4.04 kg/m$^2$ and for HD participants 23.8 kg/m$^2$. As one can see, they did not differ much in terms of overall weight and BMI for each group and gender within the group. The median BMI category for the total study population was category 4 (normal), of which the minimum was category 3 (Grade I PEM) and category 2 (Grade II PEM) and maximum category 5 (class I obesity) and category 6 (class II obesity) for PD and HD respectively. The waist circumference was only measured in the HD group, and the mean thereof for females was 84.4 cm (56–136 cm, of which three were >88 cm) and 86.9 cm (66–123 cm) for men, of which four were >102 cm). Overall average for all HD participants was 88.1±16.04 cm. During the course of the study, there were no significant changes seen in the participants' anthropometric assessment.

**Table 16:** Anthropometrical results of participants (n=36 for PD, and n=37 for HD)

| | | All participants | | | PD | | | | HD | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Variables | Gender | Valid N | Mean | Range | Valid N | Mean | Range | SD | Valid N | Mean | Range | SD |
| Weight (kg) | Males & females | 73 | 65.18 | 35 – 105 | | | | | | | | |
| | Males | | | | 16 | 63.3 | 54.8 - 105 | 12.9 | 19 | 65.5 | 35 - 101 | 16.6 |
| | Females | | | | 20 | 63 | 44.5 - 91.5 | 12.9 | 18 | 57.6 | 42 - 105 | 16.6 |
| BMI (kg/m2) | Males & females | 73 | 23.85 | 14.2 - 38.6 | | | | | | | | |
| | Males | | | | 16 | 23.1 | 17.4 - 30 | 4.0 | 19 | 23.4 | 14.2 - 33.4 | 4.9 |
| | Females | | | | 20 | 24.8 | 18.3 - 32.4 | 4.0 | 18 | 22.6 | 16.8 - 38.6 | 4.9 |
| BMI category (1-7) | Males & females | 73 | 4 | 2 - 6 | | | | | | | | |
| | Males | | | | 16 | 4 | 3 - 6 | n/a | 19 | 4 | 2 - 6 | n/a |
| | Females | | | | 20 | 4 | 4 - 6 | n/a | 18 | 4 | 2 - 7 | n/a |
| WC (cm)* | Males & females | 73 | 88.08 | 56 - 136 | | | | | | | | |
| | Males | | | | n/a | n/a | n/a | n/a | 19 | 86.9 | 66 - 123 | 16.0 |
| | Females | | | | n/a | n/a | n/a | n/a | 18 | 84.4 | 56 - 136 | 16.0 |
| WC category (1-2)* | Males & females | 73 | 2 | 1 - 2 | | | | | | | | |
| | Males | | | | n/a | n/a | n/a | n/a | 19 | 2 | 2 - 1 | n/a |
| | Females | | | | n/a | n/a | n/a | n/a | 18 | 2 | 2 - 1 | n/a |

**Only applicable to HD participants*
*n/a =not applicable*

### 4.2.2. Biochemical status

The overall lipid readings tested during the course of the trial are summarised in Table 17. The average cholesterol was 4.72±1.33 mmol/l (min 2.05, max 10.16) and 3.33±0.86 mmol/L (min 0.68, max 6.07); LDL cholesterol 2.98±1.04 mmol/l (min 0.98, max 7.26) and 1.89±0.57 mmol/l (min 0.43, max 3.27); HDL cholesterol 0.98±0.3 mmol/l (min 0.31, max 2.04) and 0.95±0.32 mmol/L (min 0.1, max 2.09); and TG 1.67±0.88 mmol/l (min 0.52, max 5.6) and 1.05±0.57 mmol/l (min 0.26, max 3.27) for PD and HD participants respectively. The averages in the table vary slightly, as these include all the participants even if they did not use the required amount of sterol-enriched margarine/control margarine specified (25 g/day). When adjusting for those who consumed the necessary amount of 25 g/day, the results changed. Twenty three PD participants and 5 HD participants had elevated LDL cholesterol levels at baseline.

## 4.3. NUTRITIONAL INTAKE AND COMPLIANCE WITH GUIDELINES

The mean percentage of dietary compliance, for the total study population can be seen in Figures 7 and 8. Both figures 7 and 8 show the mean percentage of dietary compliance for the paricipants that consumed the recommended 25 g/day sterol- and control-margarine for the duration of the trial, as the intake differed when those who did not consume the recommended amount were included. The PD group went from 36 to 27, and the HD group went from 37 to 22 participants (S&C, n=49) being compared in terms of sterol effectiveness in lowering LDL cholesterol levels as a primary treatment outcome. What was noted for the PD group, in Figure 7, was that participants consumed: an excess percentage of total energy from carbohydrates per day (106-107%) with inadequate fibre intake (58-60%); less than the required amount of total fat per day (78-82%) but an excess amount of saturated fat (98-101%), cholesterol (105-112%), PUFA (104-117%) and inadequate amounts of MUFA (39-41%); and their overall total energy (78-92%) and protein per ideal body weight intake (78-81%) was inadequate according to the K/DOQI and TLC guidelines for patients receiving PD. What was noted for the HD group, in Figure 8, was that the participants consumed an inadequate percentage of total energy from carbohydrates per day (90-92%) with inadequate fibre intake (67-71%); an excess amount of total fat per day (112-113%) with an excess amount of saturated fat (111-112%) and PUFA (131-136%), and less than the required amounts of cholesterol (71-84%), and MUFA (43%); and the participants' overall total energy (72-75%) and protein per ideal body weight (73-74%) intake was inadequate according to the K/DOQI and TLC guidelines for patients receiving HD.

There were slight changes between the arms in the trial compared to those measured during the baseline stage (all of which were statistically insignificant). For all the participants included throughout the trial and for those that used the required sterol-enriched/control margarine specified (S&C) respectively the following occurred in the PD group when using the sterol-enriched margarine, the total energy increased by 1.7 g/kg IBW, carbohydrate intake decreased by 5.7 and 3% TE, total fat percentage increased by 4.8 and 3.6%, saturated fat intake increased by 0.9 and 0.6%, cholesterol intake increased by 12.7 and 23.4 mg per day, PUFA increased by 7.2 and 5.2% TE, MUFA increased by 7.2 and 5.2%, fibre intake decreased by 0.2 and 0.7 g per day, and protein intake (g/IBW) remained constant (1 g/kg IBW). When the PD group used the control margarine, the TE increased by 0.2 g/kg ideal body weight (decreased by 3.1 g/kg IBW for those using S&C), carbohydrate intake decreased by 4.2 and increased by 1.1% TE in the S&C group, total fat percentage increased by 4 and 1.5%, saturated fat intake increased by 0.8% and remained the same in the S&C group, cholesterol intake increased by 10.9 and 26.2 mg per day, PUFA increased by 6.5 and 4.5% TE, MUFA increased by 1.1 and 0.2%, fibre intake increased by 0.9 and decreased by 1.5 g per day in the S&C group, and protein intake (g/kg IBW) remained constant (1 g/kg IBW) for all the participants included throughout the trial and for those who used the required sterol-enriched/control margarine specified (S&C) respectively. In the HD group, when using the sterol-enriched margarine, the total energy increased by 2.2 and 3.4 g/kg IBW, carbohydrate intake increased by 1.9 and 1.1% TE, total fat percentage increased by 0.5 and 1.5%, saturated fat intake decreased by 1.2 and 0.9%, cholesterol intake decreased by 17.8 and 9.6 mg per day, PUFA increased by 5.5 and 7.3% total energy, MUFA decreased by 1.1 and 1%, fibre intake decreased by 3.4 and 4 g per day, and protein intake (g/kg IBW) remained constant (0.9 g/kg IBW) for all the participants included throughout the trial and for those that used the required sterol-enriched/control margarine specified (S&C) respectively. When the HD group used the control margarine, the total energy increased by 3.6 and 4.4 g/kg IBW, carbohydrate intake increased by 4.3 and 2.9% TE, total fat percentage increased by 0.8 and decreased by 0.3%, saturated fat intake decreased by 1.6%, cholesterol intake decreased by 8.3 and 5 mg per day, PUFA increased by 6 and 6.9% TE, MUFA decreased by 1.61%, fibre intake decreased by 1.3 and 2.5 g per day, and protein intake (g/kg IBW) remained constant (0.9 g/kg IBW) for all the participants included throughout the trial and for those that used the required sterol-enriched/control margarine specified (S&C) respectively. These small changes throughout the trial can be seen in Figure 7 and 8 (for all participants) and Figures 9 to 17 (including S&C), where PD and HD groups are illustrated separately on each graph and the numbering on these bars indicate the sequence of in which the events occurred (baseline, provision of sterol margarine, washout, and provision of control margarine).

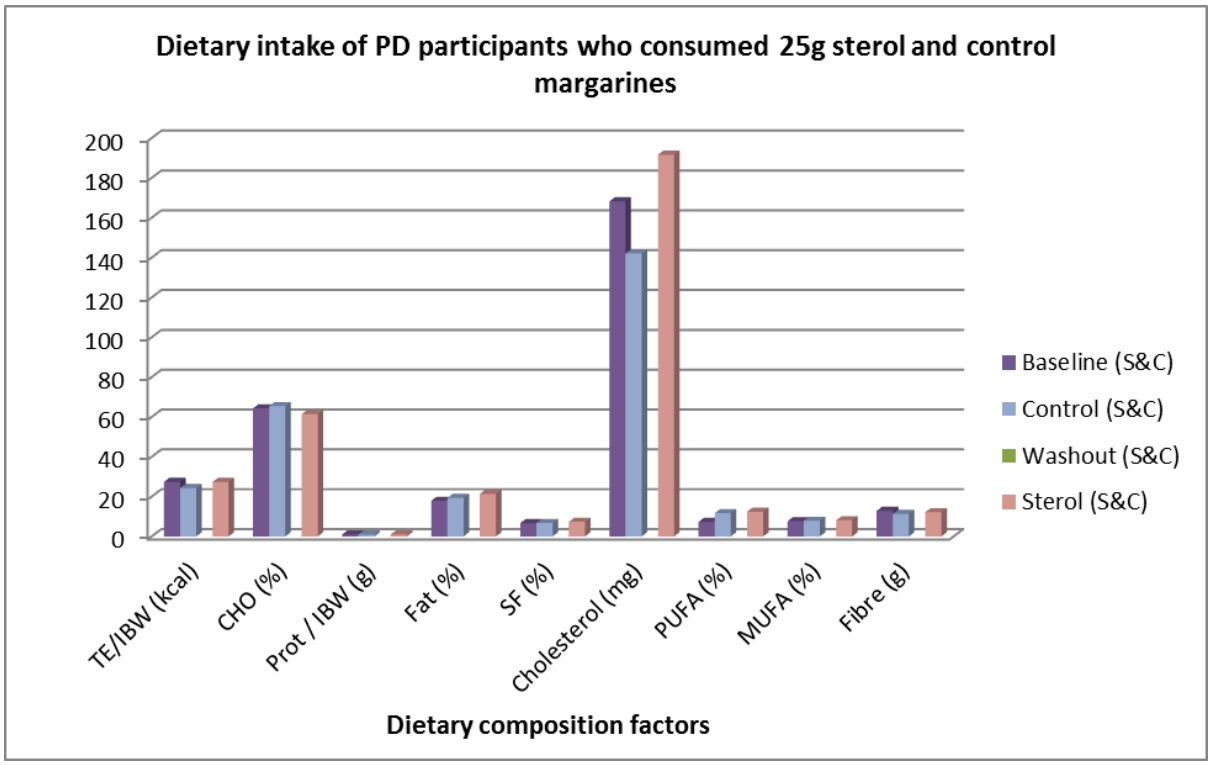
**Table 17:** Lipid profiles of PD and HD patients

| | PD (36) – received control then sterol | | | | HD (37) - received sterol then control | | | |
|---|---|---|---|---|---|---|---|---|
| | **Cholesterol mmol/L** | **HDL mmol/L** | **Triglycerides mmol/L** | **LDL mmol/L** | **Cholesterol mmol/L** | **HDL mmol/L** | **Triglycerides mmol/L** | **LDL mmol/L** |
| **Baseline total*** | **4.42** | **0.94** | **1.49** | **2.81** | **3.25** | **0.98** | **0.94** | **1.85** |
| Post control | 4.80 | 1.01 | 1.69 | 3.02 | 3.55 | 1.04 | 1.06 | 2.03 |
| **Including only those that consumed 25g/d (control, n=27 for PD, and n=22 for HD)**** | **4.79** | **0.99** | **1.74** | **3.00** | **3.51** | **1.06** | **1.07** | **1.95** |
| Post washout | 4.71 | 1.03 | 1.67 | 2.92 | 3.03 | 0.80 | 1.12 | 1.71 |
| Post sterol | 4.83 | 0.93 | 1.78 | 3.09 | 3.49 | 1.00 | 1.06 | 2.00 |
| **Including only those that consumed 25g/d (sterol, n=27 for PD, and n=22 for HD)**** | **4.61** | **0.97** | **1.55** | **2.94** | **3.26** | **0.91** | **1.04** | **1.87** |
| Interpretation comparing control to sterol | ↑ to ↓ | ↑ to ↓ | ↑ to ↓ | ↑ to ↓ | ↑ to ↓ | ↑ to ↓ ($p<0.01$) | ↑ to ↓ | ↑ to ↓ |
| Recommended 'target' level according to TLC guidelines | <5.17 | >1.03 | < 1.5 / non HDL < 3.4 | <2.59 | <5.17 | >1.03 | < 1.5 / non HDL < 3.4 | <2.59 |

**Of the 36 PD participants included and analysed, 23 had elevated baseline LDL and total cholesterol levels. Of the 37 HD participants included and analysed, 4 had elevated baseline LDL and total cholesterol levels.*

***The total number of patients reduced from n = 36 to n = 27 in PD; and from n = 37 to n = 22 in the HD group when assessing for those that consumed the recommended amount throughout the trial*

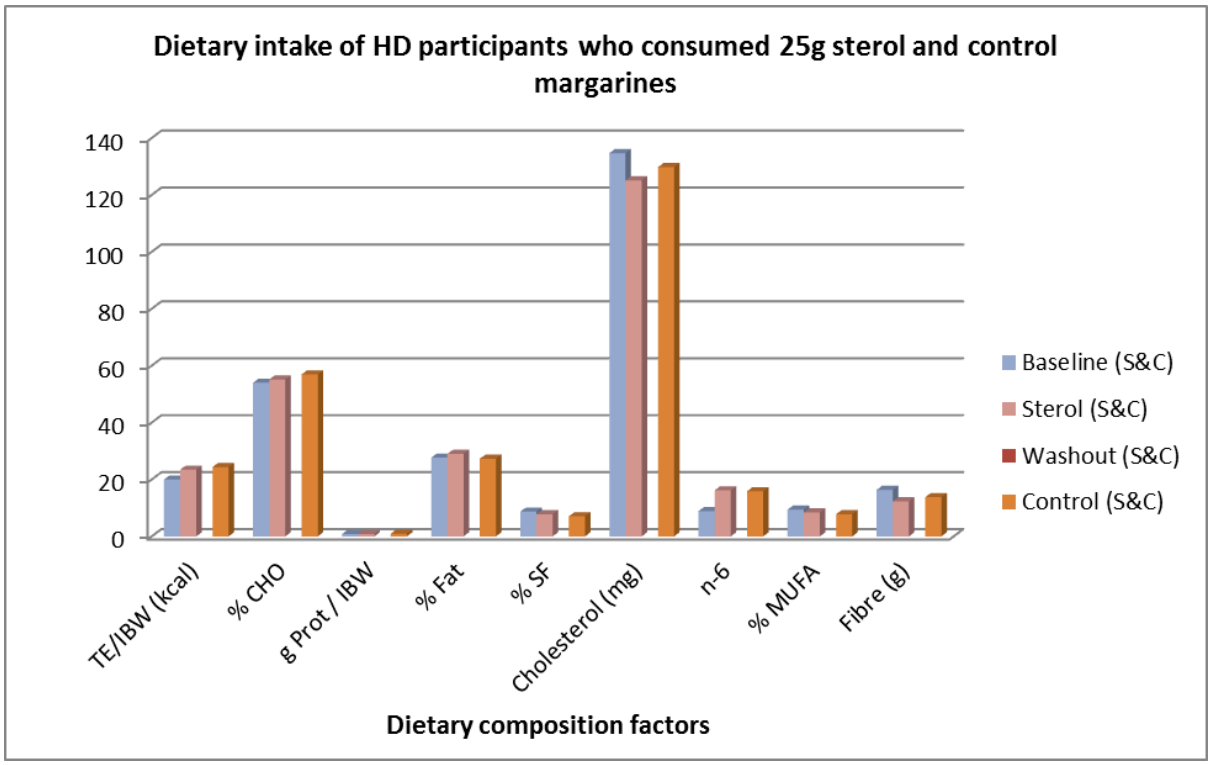
In summary when comparing the PD and HD groups, the TE intake per kg IBW increased in the HD group; percentage carbohydrate intake decreased in the PD and increased in the HD group of which the fibre intake in the PD group decreased slightly but the HD group had a larger decrease in their fibre intake; total percentage of fat intake increased in the PD group but increased slightly in the HD group of which the saturated fat, total cholesterol and MUFA intake increased in the PD group but decreased in the HD group; and finally both had a much higher PUFA intake (Figure 9 to 17 below).




| **PD** (total n=36 ,S&C n=27) | TE/IBW[a] (kcal) | CHO[b] (%) | Protein/ IBW[c] (g) | Fat (%) | SF[d] (%) | Cholesterol (mg) | PUFA[e] (%) | MUFA[f] (%) | Fibre (g) |
|---|---|---|---|---|---|---|---|---|---|
| AIM | 30-35 | 50-60 | 1.2-1.3 | 25-35 | <7 | <200 | <10 | ≤20 | 20-25 |
| Mean S&C* | 26.3 | 63.7 | 0.9 | 19.5 | 6.9 | 167.3 | 10.4 | 7.8 | 12.1 |
| % of mean S&C* | 88 | 106 | 78 | 78 | 98 | 84 | 104 | 39 | 60 |
| Mean (total) | 26.4 | 64.4 | 1.0 | 20.6 | 7.1 | 158.1 | 11.7 | 8.2 | 11.5 |
| % of mean | 88 | 107 | 81 | 82 | 101 | 79 | 117 | 41 | 58 |

*TE/IBW[a]: Total energy per ideal body weight; CHO[b]: Carbohydrate; Protein/IBW: Protein per ideal body weight; SF[d]: Saturated fat; PUFA[e]: Polyunsaturated fatty acids; MUFA[f]: Monounsaturated fatty acids*
**Included only those participants that used the specified 25g of Control and or Sterol-enriched margarine during the course of the trial*

**Figure 7:** Dietary intake of only those participants that consumed the specified 25g of margarine provided, according to TLC and KDOQI requirements for ESRD patients receiving PD




| **HD** (total n=37 ,S&C n=22) | TE/IBW[a] (kcal) | CHO[b] (%) | Protein/ IBW[c] (g) | Fat (%) | SF[d] (%) | Cholesterol (mg) | PUFA[e] (%) | MUFA[f] (%) | Fibre (g) |
|---|---|---|---|---|---|---|---|---|---|
| AIM | 30-35 | 50-60 | 1.2 | 25-35 | <7 | <200 | <10 | ≤20 | 20-25 |
| Mean S&C* | 22.6 | 55.3 | 0.9 | 28.0 | 7.8 | 129.8 | 13.6 | 8.5 | 14.1 |
| % of mean S&C* | 75 | 92 | 74 | 112 | 112 | 65 | 136 | 43 | 71 |
| Mean (total) | 21.5 | 54.3 | 0.9 | 28.2 | 7.8 | 141.3 | 13.1 | 8.6 | 13.4 |
| % of mean | 72 | 90 | 73 | 113 | 111 | 71 | 131 | 43 | 67 |

*TE/IBW[a]: Total energy per ideal body weight; CHO[b]: Carbohydrate; Protein/IBW: Protein per ideal body weight; SF[d]: Saturated fat; PUFA[e]: Polyunsaturated fatty acids; MUFA[f]: Monounsaturated fatty acids*

**Included only those participants that used the specified 25g of Control and or Sterol-enriched margarine during the course of the trial*

**Figure 8:** Dietary intake of only those participants that consumed the specified 25g of margarine provided, according to TLC and KDOQI requirements for ESRD patients receiving HD

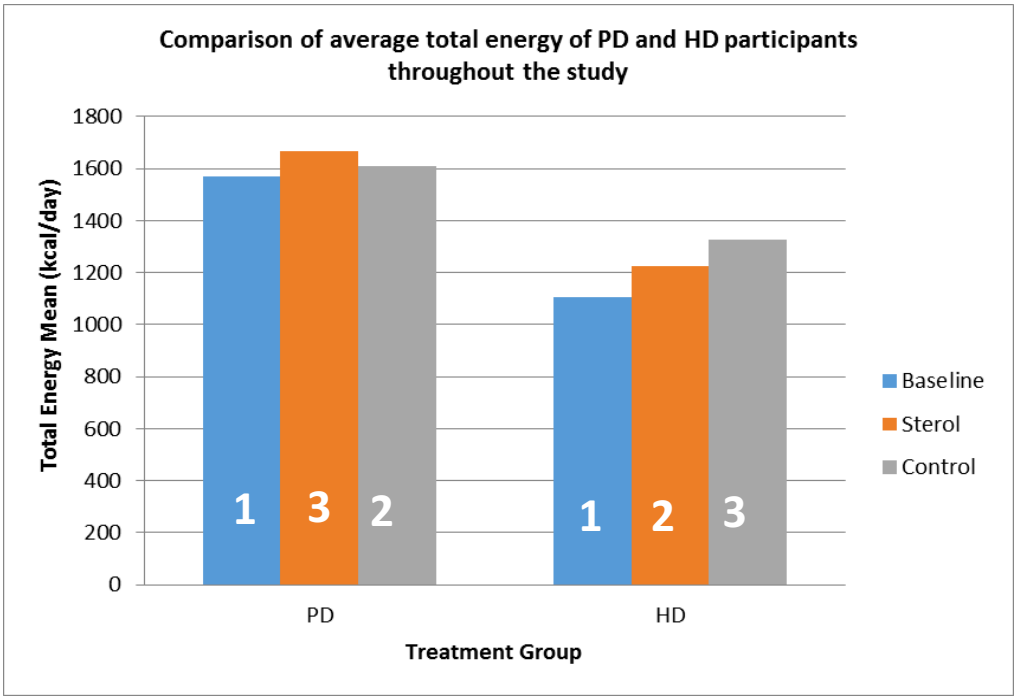



**Figure 9:** Average total energy comparison throughout the study for PD and HD participants (expressed in kcal/day) ($p<0.60$, 95%CI; $p<0.03$, 95%CI respectively)

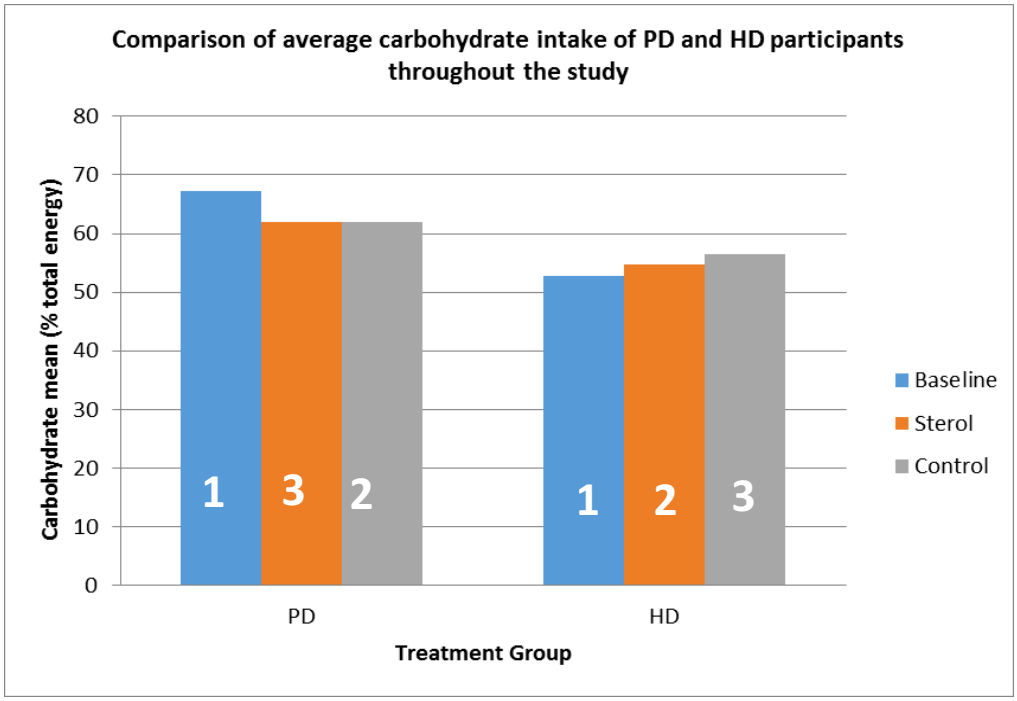



**Figure 10:** Average Carbohydrate comparison throughout the study for PD and HD participants (expressed in grams/day) ($p<0.13$, 95%CI; $p<0.23$, 95%CI respectively)

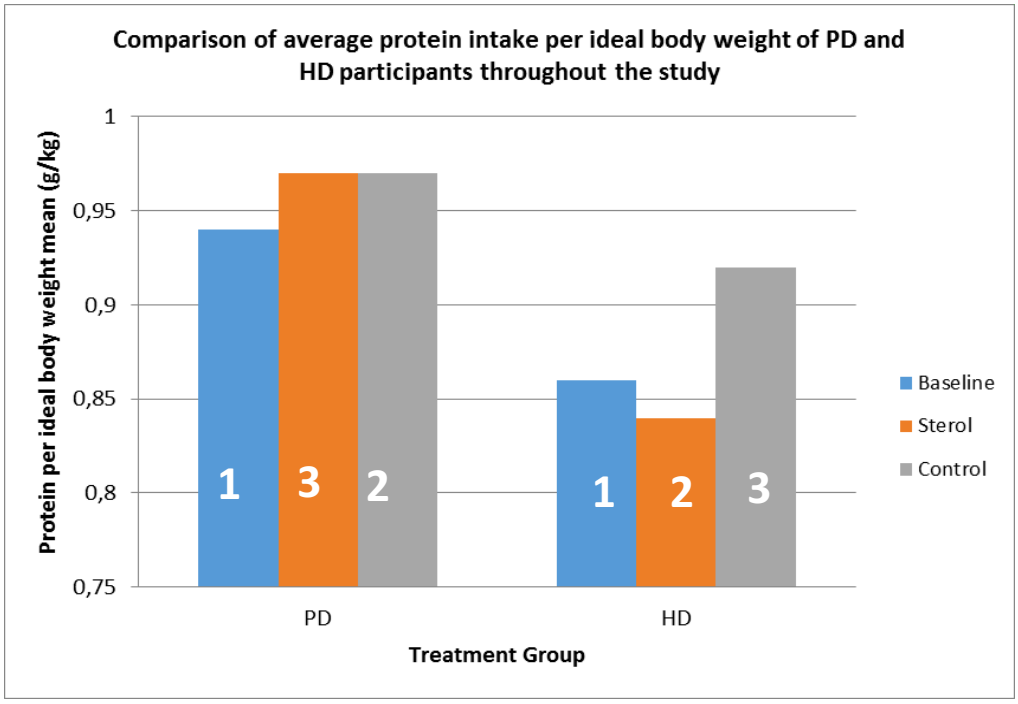



**Figure 11:** Average Protein Intake per Ideal Body Weight comparison throughout the study for PD and HD participants (expressed in grams/kg/day) (p<0.90, 95%CI; p<0.67, 95% CI respectively)

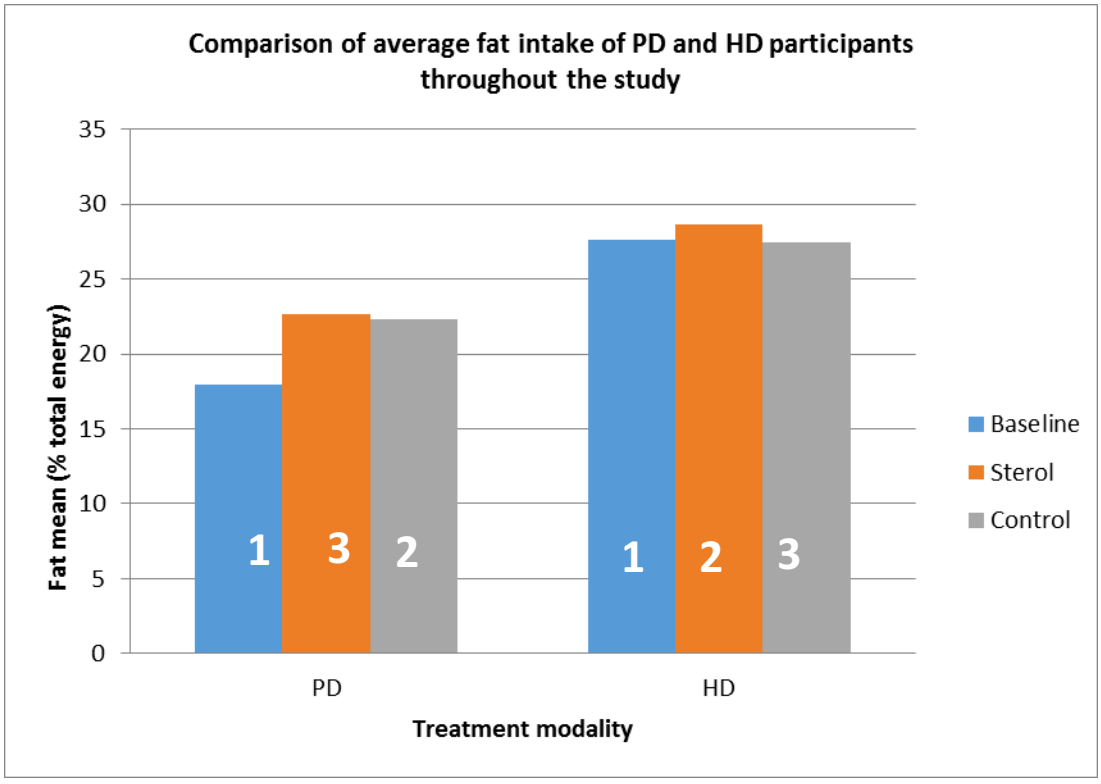



**Figure 12:** Average Total Fat intake comparison throughout the study for PD and HD participants (expressed in percentage total energy/day) (p<0.009, 95%CI; p<0.73, 95% CI respectively)

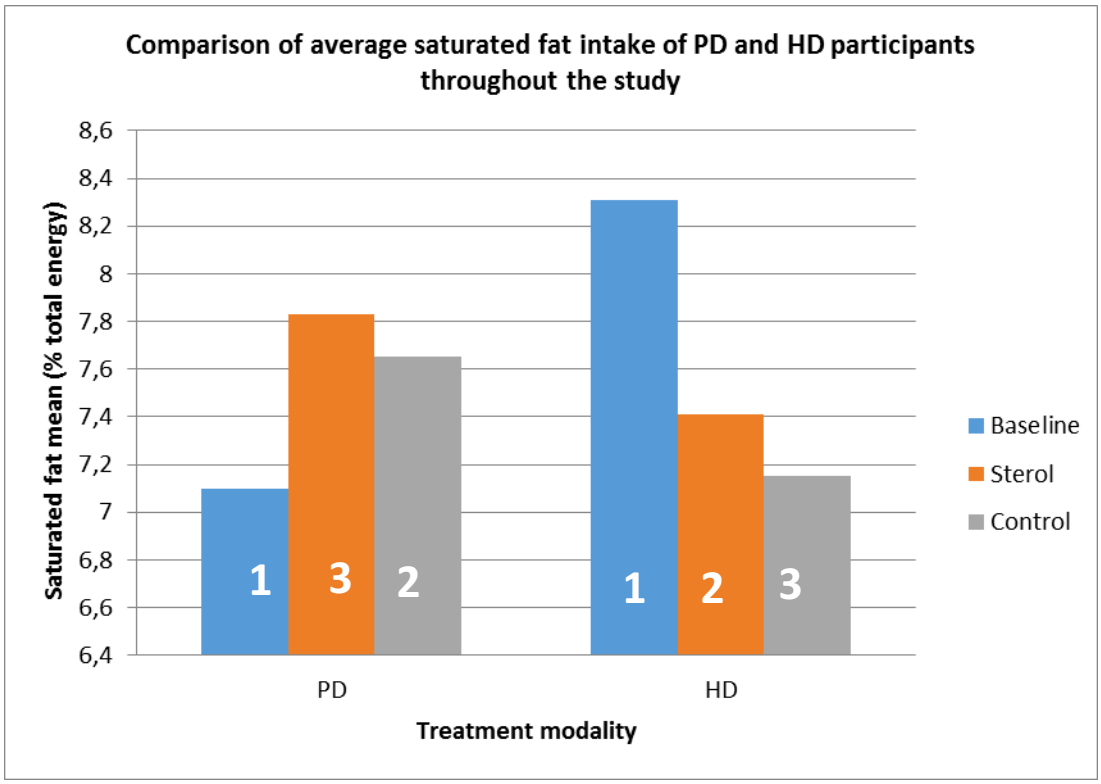



**Figure 13:** Average Total Saturated Fat intake comparison throughout the study for PD and HD participants (expressed in percentage total energy/day) (p<0.52, 95%CI; p<0.14, 95%CI respectively)

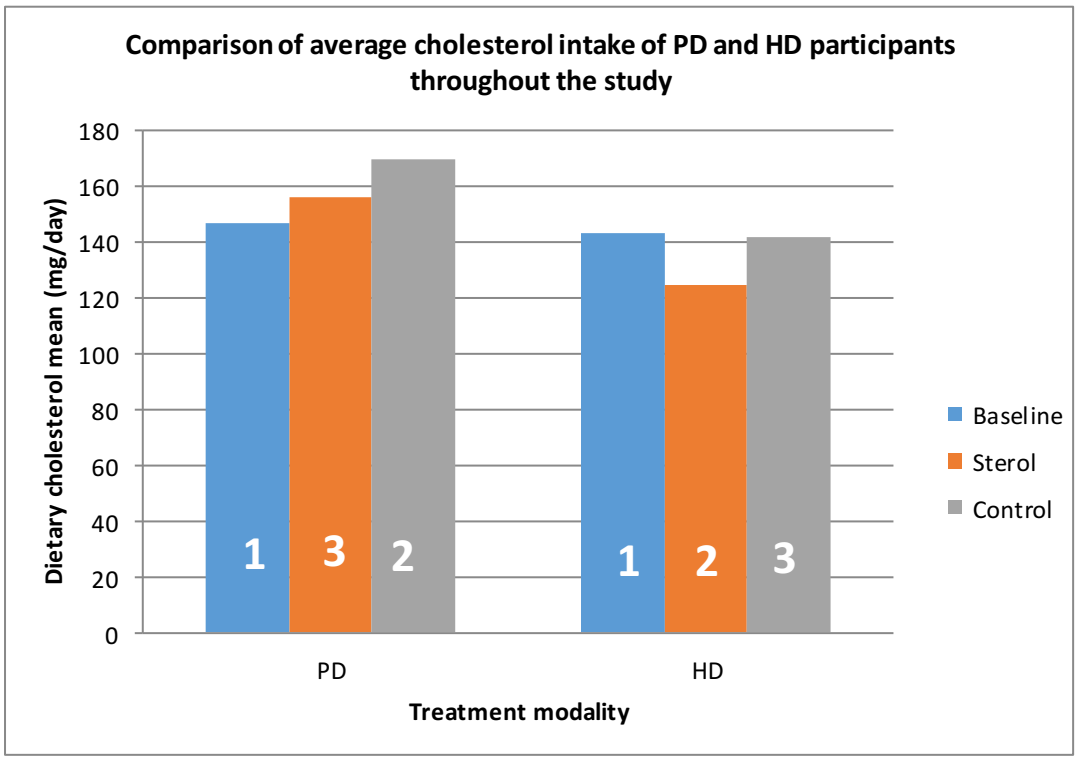



**Figure 14:** Average Total Cholesterol intake comparison throughout the study for PD and HD participants (mg/day) (p<0.74, 95%CI; p<0.78, 95%CI respectively)

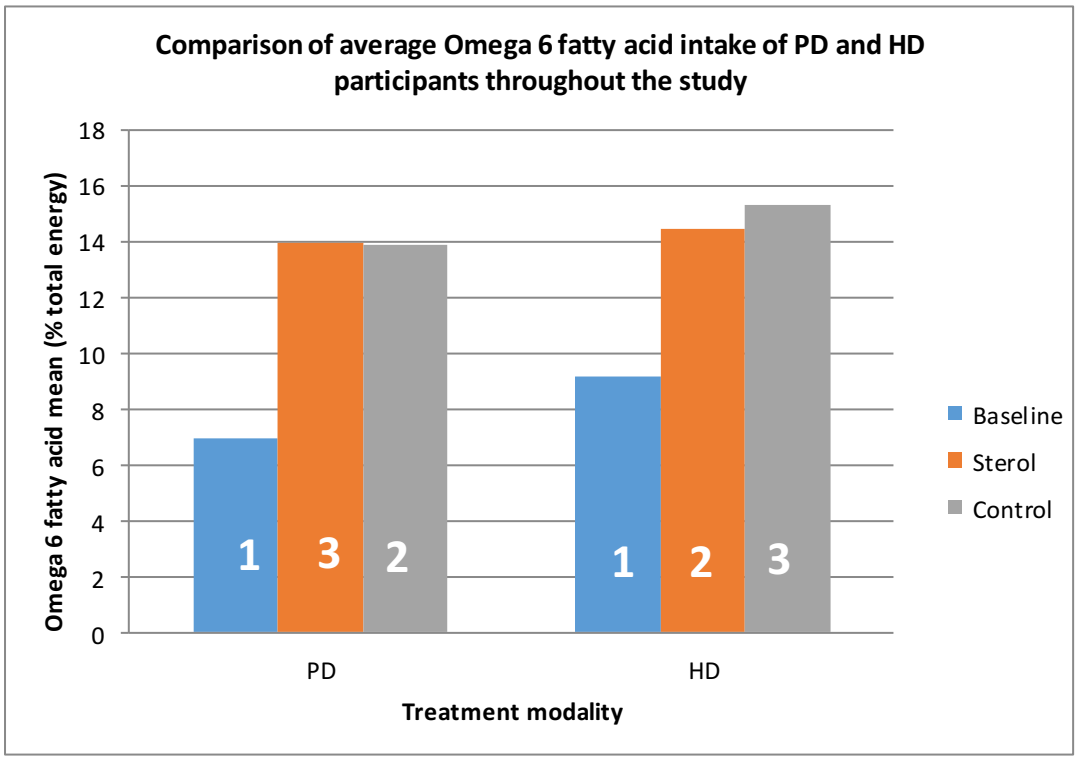



**Figure 15:** Average Omega 6 fatty acid intake comparison throughout the study for PD and HD participants (percentage total energy/day) (p<0.00001, 95%CI; p<0.00048, 95%CI respectively

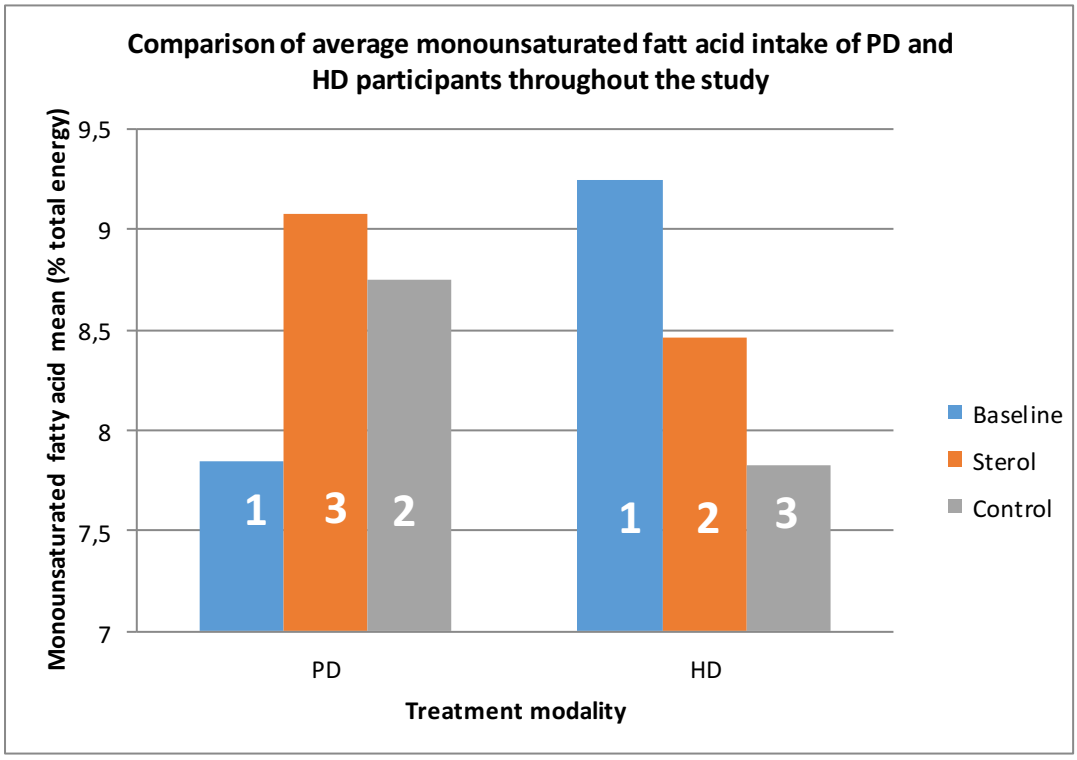



**Figure 16:** Average Monounsaturated Fatty Acid intake comparison throughout the study for PD and HD participants (percentage total energy/day) (p<0.15, 95%CI; p<0.89, 95%CI respectively**)**

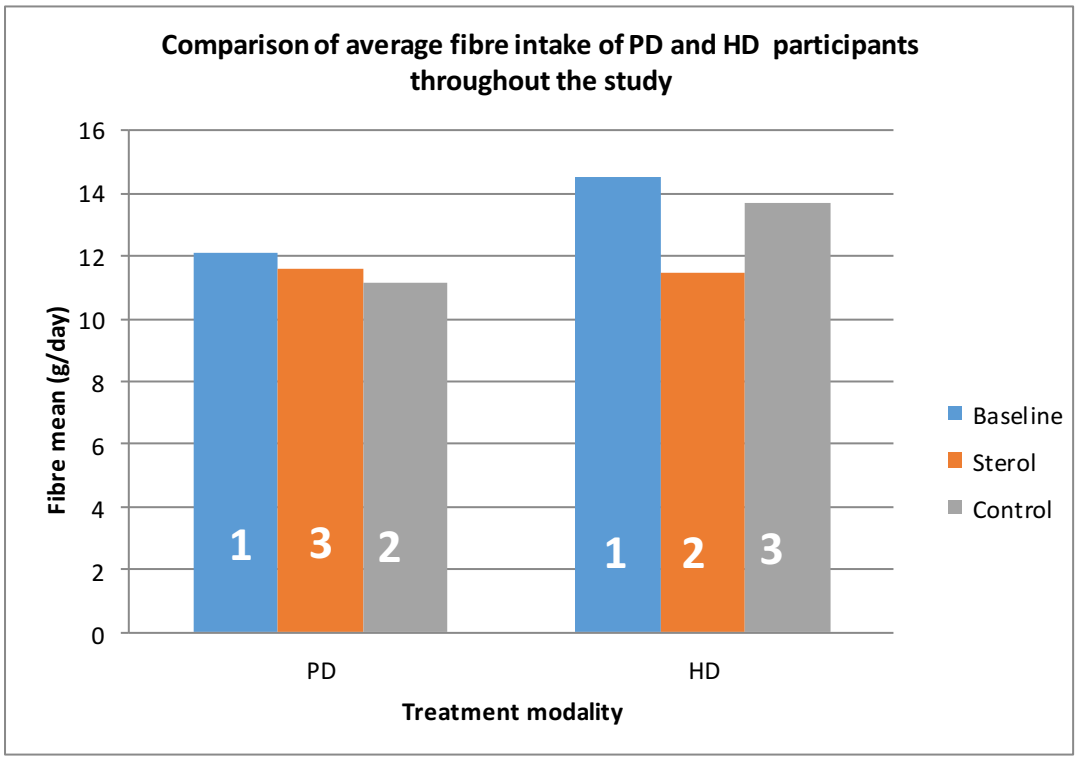



**Figure 17:** Average fibre intake comparison throughout the study for PD and HD participants (g/day) ($p<0.73$, 95%CI; $p<0.38$, 95%CI respectively)

### 4.4. EFFECT OF PLANT STEROLS

In order to determine whether the sterol intake had an influence on the respective levels of serum lipids, we completed regression analyses for each of the participants that consumed the 25 g of Sterol-enriched margarine and or control margarine where given during the course of the trial.

The baseline lipid profile for PD and HD groups differed, with PD showing a more lipemic blood profile. During the course of the trial, one could see that the allocated 8 weeks of trial and 4 weeks of washout period may have been insufficient, as the effects of either the control margarine and sterol margarine in the PD and HD groups respectively continued into the washout period of the trial, which can be seen for each of the lipid values measured in Figures 18 to 21 below. The numbers (‘1’ to ‘4’) indicated on the bars reflect the sequence of events (baseline, provision of sterol margarine, washout period, and provision of control margarine).

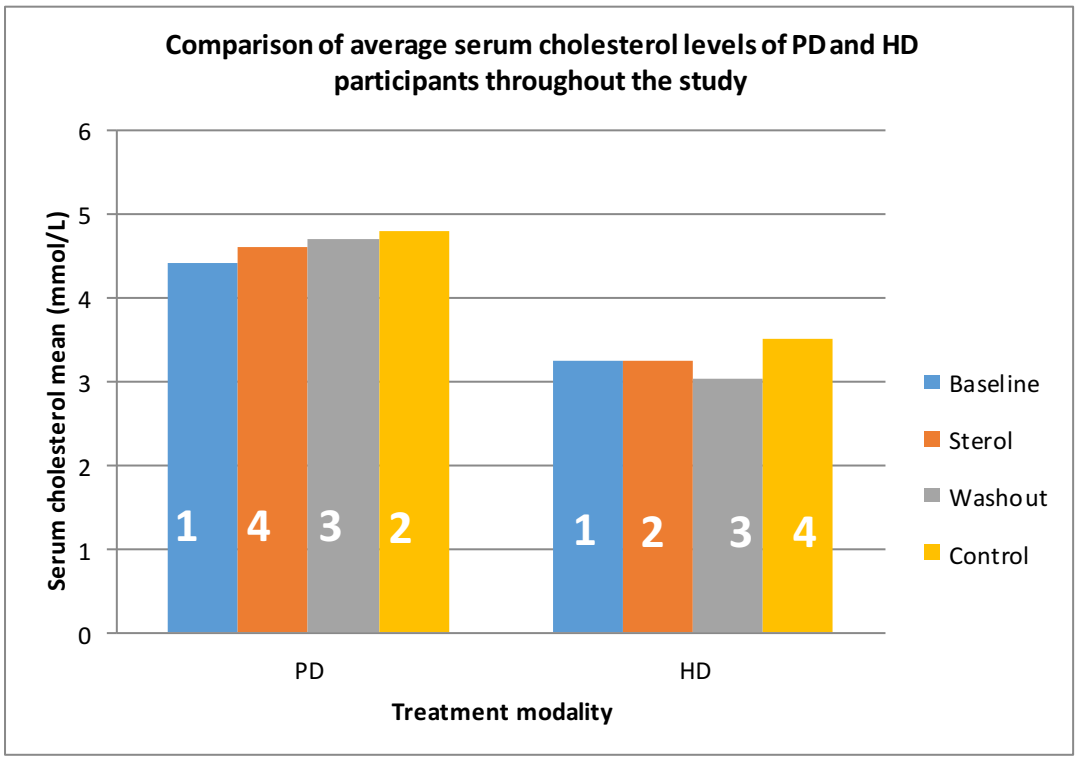



**Figure 18:** Comparison of average serum total cholesterol levels of PD and HD participants who consumed the specified amount of sterol and control margarine throughout the trial

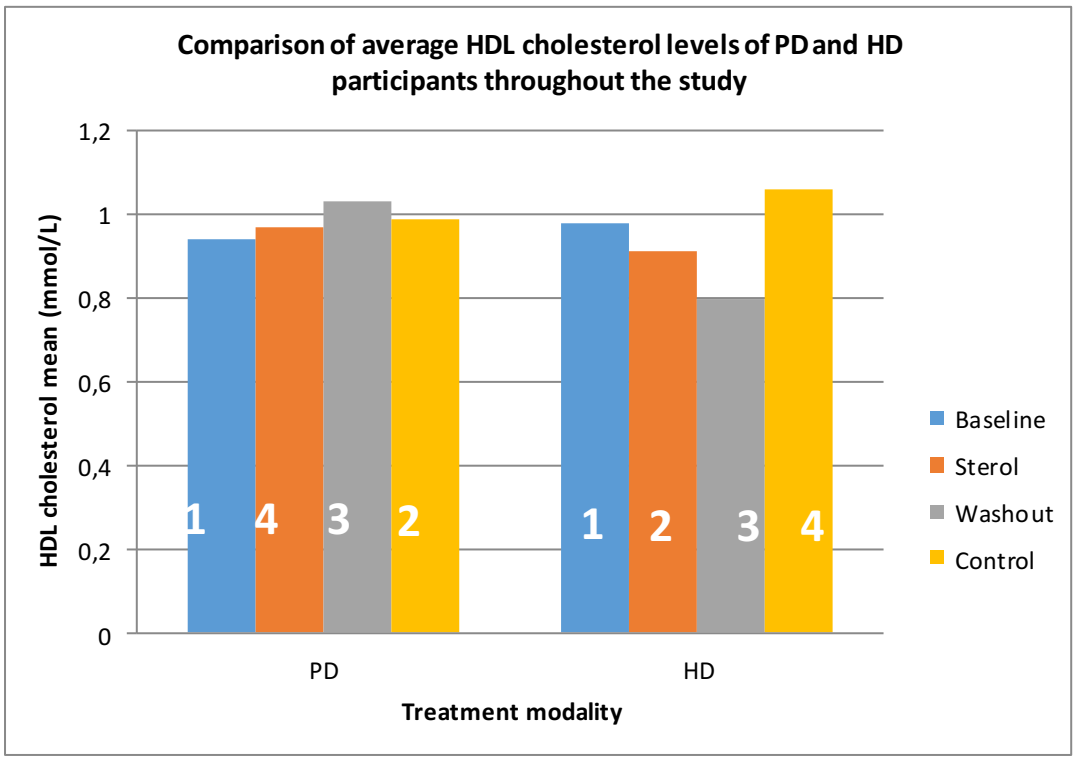



**Figure 19:** Comparison of average serum HDL cholesterol levels of PD and HD participants who consumed the specified amount of sterol and control margarine throughout the trial

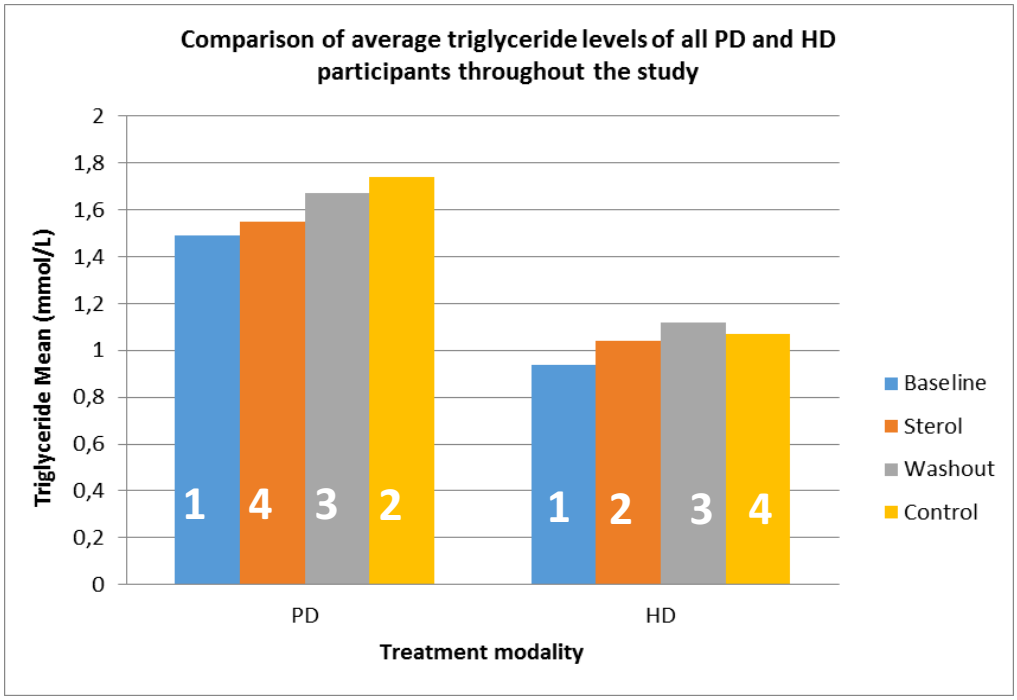



**Figure 20:** Comparison of average serum triglyceride levels of PD and HD participants who consumed the specified amount of sterol and control margarine throughout the trial

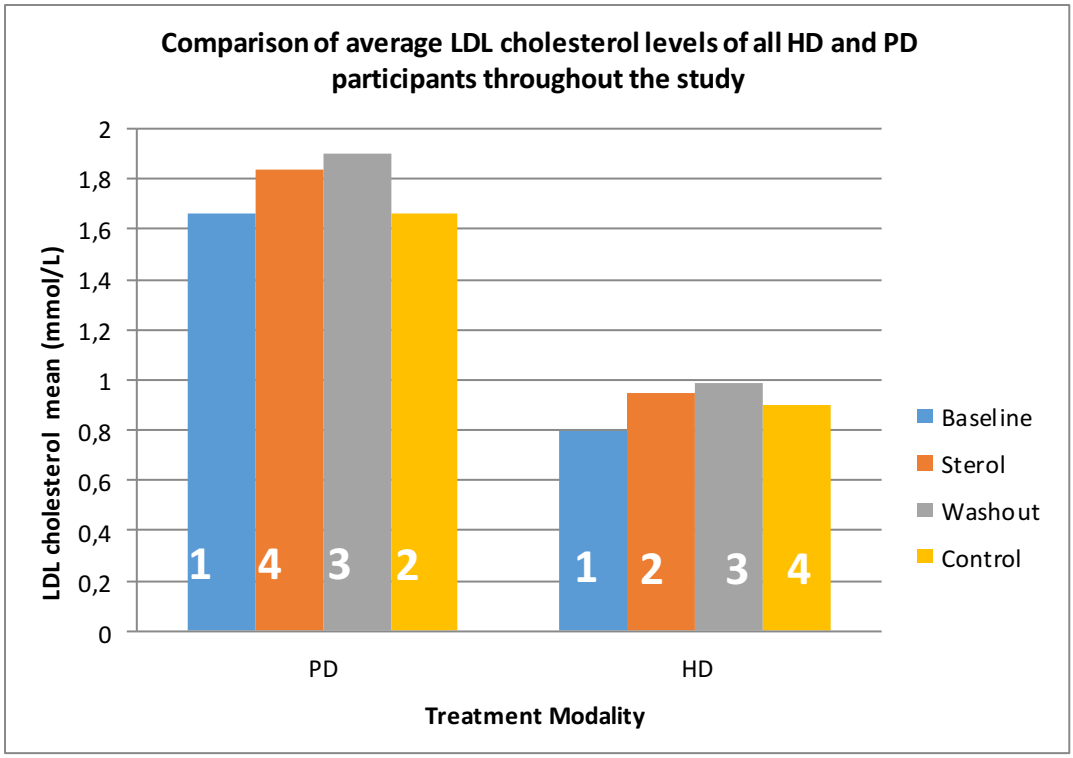


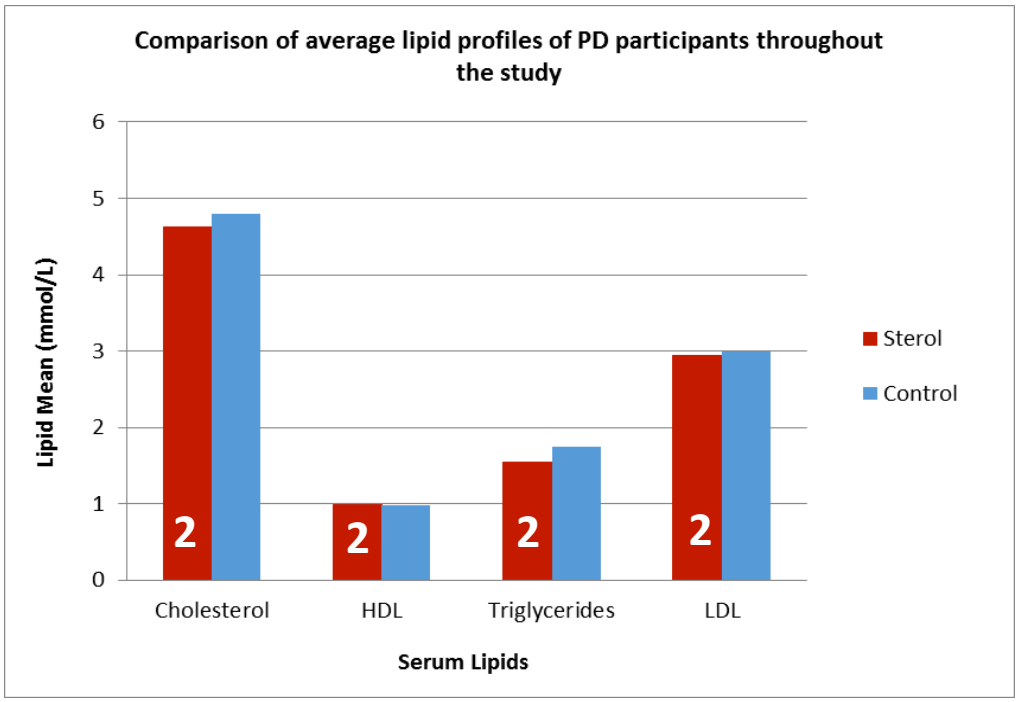

**Figure 21:** Comparison of average serum LDL cholesterol levels of PD and HD participants who consumed the specified amount of sterol and control margarine throughout the trial

For the PD group total cholesterol decreased by 0.1 mmol/l (2%), HDL decreased by 0.06 mmol/l (5%), TG decreased by 0.12 mmol/l (7.2%), and LDL cholesterol increased by 0.02 mmol/L (0.7%) - thus remained unchanged for eight weeks of trial when comparing participants using sterol-enriched margarine and control margarine (not compared to baseline readings, but rather to that of the washout period which became their baseline) as the control had an effect on their lipid levels post baseline, which did not return to normal within the washout period. All seen in Table 17 and Figures 18 to 21 above. The level of significance (– p values) was not measured as this was not what was compared, but rather done for S&C comparisons below.

For the HD group the effects of the sterol margarine may have continued into the washout period, possibly showing that the length of trial was insufficient. Their total cholesterol initially increased by 0.21 mmol/l (0.03%) but when compared to the washout results it reduced by 0.22 mmol/l (6.8%, p=0.16). The same could be seen for the other lipid levels measured, namely the HDL cholesterol decreased by 0.07 mmol/l (7.1%) versus post washout by 0.18 mmol/l (18.4%), TG increased by 0.1mmol/l (0.6%) versus post washout it decreased by 0.18 mmol/l (19.1%), and LDL cholesterol increased by 0.02 mmol/l (1%) versus post washout where it decreased by 0.14 mmol/l (7.6%). All seen in Table 17 and Figures 18 to 21 above.

Based on these effects of both the sterol and control margarine seen above, a comparison of the sterol and control (S&C) lipid levels were done for PD and HD groups separately. The aim was to show the effect of the sterol within the margarine provided and not of the margarine itself. This can be seen in Table 17 above and Figures 22 and 23 below where each of the lipids (total cholesterol, LDL cholesterol, HDL cholesterol, and TG) assessed are compared separately for PD and HD participants. The numbers indicated within the bar on Figures 22 and 23 depicts when the sterol margarine was provided, i.e. '1' indicates that the sterol enriched margarine was given directly after baseline levels were measured, and '2' indicates it was given after the washout period of the trial. When interpreting these findings, a positive effect was noted. The percentage difference in lipid levels for the PD group (n=27) was a decrease in total cholesterol by 3.7% (0.18 mmol/l, p=0.66), LDL cholesterol decreased by 2% (0.06mmol/l, p=0.89), HDL cholesterol decreased by 2% (0.02 mmol/l, p=0.73), and TG decreased by 10.9% (0.19 mmol/l, p=0.25). Whereas, in the HD group (n=22) similar findings were present as total cholesterol decreased by 7.1% (0.25 mmol/l, p=0.16), LDL cholesterol decreased by 4.1% (0.08mmol/l, p=0.52), HDL cholesterol decreased by 14.2% (0.15 mmol/l, p<0.01), and TG decreased by 2.8% (0.03 mmol/l, p=0.76); none of these were statistically significant, except for the decrease in HDL cholesterol in HD participants that was significantly lower with sterol intake.

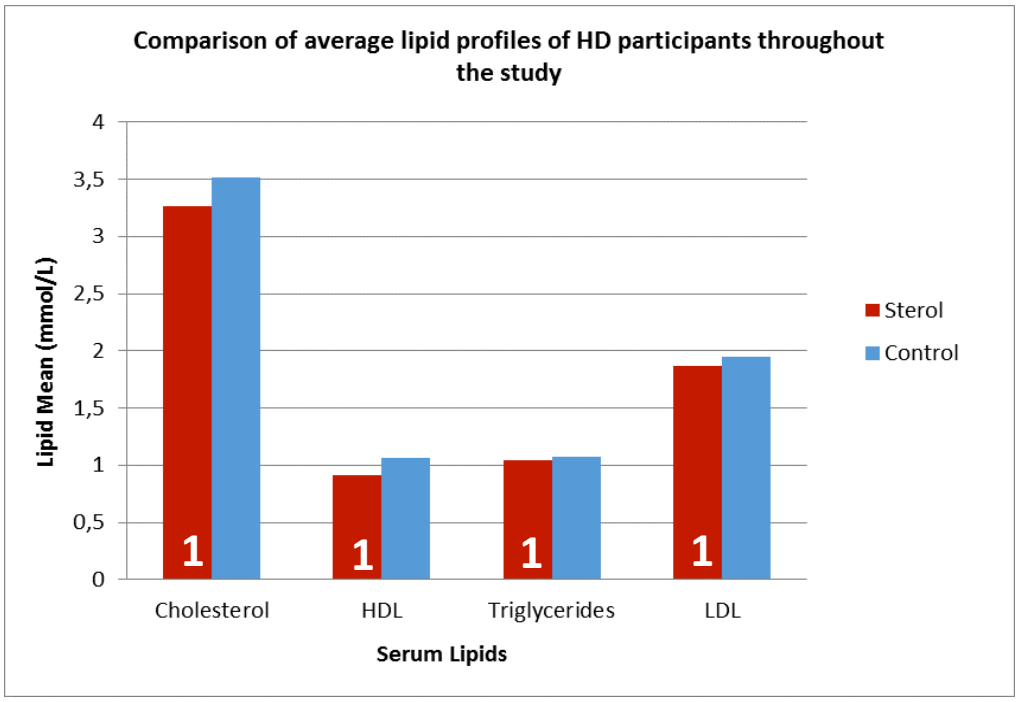
It is important to note the sequence of events within the trial for both PD and HD groups respectively when interpreting the results, which could also be related to their dietary intake which changed throughout the trial as all of these factors are interrelated when assessing the results obtained. A summary of this can be seen in Table 18.




*PD n=27;*

*Total cholesterol decreased by 3.7% (p=0.18); HDL cholesterol decreased by 2% (p=0.73); Triglycerides decreased by 10.9% (p=0.25); and LDL cholesterol decreased by 2% (p=0.89)*

**Figure 22:** Comparison of sterol and control total cholesterol, HDL cholesterol, Triglycerides and LDL cholesterol levels for PD participants who consumed the required amount of control margarine and sterol margarine given




*PD n=22;*

*Total cholesterol decreased by 7.1% (p=0.16); HDL cholesterol decreased by 14.2% (p<0.01); Triglycerides decreased by 2.8% (p=0.76); and LDL cholesterol decreased by 4.1% (p=0.52)*

**Figure 23:** Comparison of sterol and control total cholesterol, HDL cholesterol, Triglycerides and LDL cholesterol levels for HD participants who consumed the required amount of control margarine and sterol margarine given

Both groups illustrated a decrease in both LDL cholesterol and total cholesterol, even though not statistically significant due to sample size (RMSSE 64% and 71% for PD and HD groups respectively); but the difference in the extent of the values (PD having much higher readings versus HD) could be expected when looking at the literature in terms of treatment modality.

**Table 18:** Summary of individual diet variables and the effect thereof on lipid levels measured throughout the trial as an adjunct to sterol use

| Treatment modality | *How it changed during the course of the trial* | Protein (g per IBW) | Carbohydrate | | Fat | | | | | Total energy (kcal per IBW) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Total (%) | Fibre (g)*** | Total (%) | Saturated fat (%)*** | MUFA (%) | PUFA, specifically n-6 (%)*** | Cholesterol (mg)*** | |
| PD | Changes noted | Increased slightly | Decreased during the control and sterol arms of the trial (equivalent) | Decreased slightly in the control, then increased slightly after the sterol arm of the trial | Increased during the control and sterol arms of the trial (equivalent) | Increased in the control and thereafter continued to increase in the sterol arm of the trial | Increased as the trial progressed from control to sterol arm of the trial | Increased during the control and sterol arms of the trial (equivalent) | Increased during the control and thereafter slightly decreased in the sterol arm of the trial (equivalent) | Progressively increased as the trial progressed but ever so slight |
| | Possible reasoning | Less years on treatment is linked to increased compliance with dietary counceling from the more frequent dietetic interaction during the course of the trial as they aim to improve their nutritional value of their diet.** Feel like they have control / autonomy over their diets. Less mixed messages are given to the patient re dietary intake from the MDT. | | | Possibly with increased protein intake (saturated fat increased) and provision of margarine (PUFA increased) | With increased protein intake | Anomily as most foods rich in MUFA are not allowed with their electrolyte content. | Margarine provided is a rich source of PUFA, specifically n-6 | | Consumed more protein & fat in place of carbohydrate |
| | Overall nutritional composition of diet | 78% of mean (0,9 g/kg ideal body weight per day) | 106% Of the maximum requirements consumed & obtained from the dialysate (63.4% of mean total energy) | 60% of mean (12.5 g/day) | 78% of the requirements consumed (19.5% of mean total energy) | 98% of mean (6.9%) | 39% of mean (7.8%) | 104% of mean (10.4%) | 84% of mean (167.3 mg/day) | 88% of requirements consumed (mean 26.4 kcal/kg ideal body weight per day) |
| | Possible effect on Lipogram results when comparing sterol and washout bloods | Increased LDL cholesterol with insufficient intake (increased losses) | | ? TG (decreased by 7,2%, 0.19 mmol/l) | Lower that favourable effectiveness of sterols as their typical diet is low in fat | ? HDL Cholesterol (5%, 0.06 mmol/l) | Non significant decrease in HDL cholesterol | ? HDL Cholesterol (5%, 0.06 mmol/l) | Decreased effectiveness of sterol relating to reduced mechanism of action | |
| | Possible effect on Lipogram results when comparing sterol and control bloods | | | ? TG (decreased by 10,9%, 0.19 mmol/l, p=0.25) | ? LDL Cholesterol (2%, 0.06 mmol/l, p=0.89) & ?total cholesterol (3.7%, 0.18 mmol/l, p=0.66) | ? HDL Cholesterol (2%, 0.02 mmol/l, p=0.73) | Non significant decrease in HDL cholesterol | ? HDL Cholesterol (2%, 0.02 mmol/l, p=0.73) | Decreased effectiveness of sterol relating to reduced mechanism of action | |
| HD | Changes noted | Decreased slightly with sterol arm of trial, thereafter increased in control arm | Icreased slightly as the trial progressed | Decreased in the sterol and increased in the control arm of the trial | Increased slightly in the sterol, and decreased back to baseline levels in the control arm of the trial | Progressively decreased during the course of the trial | Progressively decreased during the course of the trial | Progressively increased during the course of the trial* | Decreased in sterol arm and increased during control arm of the trial | Progressively increased as the trial progressed but ever so slight |
| | Possible reasoning: | Most added the margarine to sandwichs vs cooked meals. Protein is generally more expensive in comparison for the grant received, hence intake thereof is often compramised | | Consumed more refined sources of carbohydrates & possibly less fruit /vegetables | Replaced that which they were previously using with margarine provided | Butter was replaced with margarine | Anomily | Margarine provided is a rich source of PUFA, specifically n-6 | Increased as their intake of protein increased (simultaneously) | Increased with increased refined carbohydrates and fat in sterol arm versus increased intake of protein and unrefined carbohydrates during the control arm of the trial |
| | Overall nutritional composition of diet | 73% of mean (0.9 g/kg ideal body weight per day) | 92% of mean (55.3% of mean total energy) | 71% of mean (14.1 g/day) | 112% of mean (28.2% of mean total energy) | 112% of mean (8.5%) | 43% of mean (8.5%) | 136% of mean (13.6%) | 65% of mean (129.8 mg/day) | 75% of requirements (mean 21.5 g/kg ideal body weight per day) |
| | Possible effect on Lipogram results when comparing post sterol & washout and baseline bloods | | ?TG (by 10.6% and continued into washout period by 19.1%) | ?TG (by 10.6% and continued into washout period by 19.1%) | Higher effectiveness of sterols as their typical diet is higher in fat when compared to PD participants diet | ? LDL Cholesterol (increased by 1% and then decreased into the washout period by 7.6%) | | ? LDL Cholesterol (increased by 1% and then decreased into the washout period by 7.6%) & ?HDL cholesterol (decreased by 7% and continued to decrease by 18.4% into the washout period) | Increased effectiveness of sterol relating to reduced mechanism of action | |
| | Possible effect on Lipogram results when comparing sterol and control bloods | | ? TG (by 2.8%, 0.03mmol/l, p=0.76) | ? TG (by 2.8%, 0.03mmol/l, p=0.76) | Higher effectiveness of sterols as their typical diet is higher in fat when compared to PD participants diet | ? LDL Cholesterol (by 4.1%, 0.08 mmol/l, p=0.52) and ?total cholesterol (7.1%, 0.25 mmol/l, p=0.16) | | ? LDL Cholesterol (by 4.1%, 0.08 mmol/l, p=0.52) & ?total cholesterol (7.1%, 0.25 mmol/l, p=0.16) & ?HDL cholesterol (by 14.2%, 0.15 mmol/l, p<0.01) | Decreased effectiveness of sterol relating to reduced mechanism of action | |

* Lasting effect from first arm of the trial

** Mean duration of treatment years for PD 4years (1-10) & for HD 6years (1-16)

*** Overall saturated fat and cholesterol intake in both PD and HD groups were within the requirements specified according to KDOQI/KDIGO guidelines; what was noted was that a very refined diet was consumed by both these patient groups.

Those who signed up to participate wanted to improve their overall health as a result the PD participants due to the psychological structure of the study may have as a result selected better carbohydrate sources in terms of fibre composition, and of the frequent follow up with the dietician may have lead to better food choices. Another possible explanation for the differences seen in the PD group may have been related to the number of years of treatment, of which they had fewer years of treatment vs the HD group. As a result where given a sense of autonomy in terms of their diet they were more compliant.

# CHAPTER 5: DISCUSSION

## 5.1. DISCUSSION

The present study shows that even though statistically significant reductions in LDL cholesterol and total cholesterol levels were not evident with the inclusion of plant sterol-enriched margarines, a trend towards this was evident when compared to the control margarine lipid levels. Not only did LDL cholesterol and total cholesterol levels decrease, but so did the TG and HDL cholesterol levels decrease in both the PD and HD groups. The decrease in HDL cholesterol is unfavourable, especially since both PD and HD patient groups exhibit decreased baseline levels thereof as part of their typical lipid profile. This decrease in HDL cholesterol, statistically significant in the HD group, masks the clinical benefit of the decrease in specifically LDL cholesterol, a primary target for reducing the risk of atherosclerosis, as there is a direct correlation with increased HDL cholesterol and decreased CVD risk. The vector in which the sterols were provided within the participants' typical diet may have contributed to this in both the PD and HD groups. Just as the disease is complex, so is the dietary intervention in relation to creating a more cardioprotective lipid profile aimed at reducing the risk for ASCVD.

An aggressive therapeutic intervention with the main focus of treatment aimed at reducing LDL cholesterol levels (specifically by the NCEP ATP III, ACC / AHA and ESC / EAS bodies) is required to reduce the risk of ASCVD without increasing adverse effects associated with the treatment (i.e. don't always treat to target of < 2.59 mmol/l). Advocating to reduce ASCVD risk in those most likely to benefit, like CKD patients who are placed in a 'very high risk' category for CVD morbidity and mortality, using appropriate intensity of therapy.[6,9,14,15,16,17] Due to the complexity of the participants' diagnosis, they cannot be treated using 'one size fits all' form of treatment, but instead many factors need to be taken into account when determining the ideal treatment, be it dietary and / or pharmacotherapy, to improve their overall quality of life and general outcomes. One of the complexities identified, was that related to the treatment modality received. Peritoneal dialysis patients lipid profiles generally include increased total cholesterol, LDL cholesterol, TG, and decreased HDL cholesterol; whereas in HD patients which tend to have normal total and LDL cholesterol, increased TG, and decreased HDL cholesterol levels; all of which was seen in the present study with 23 of the PD and only 4 of the HD participants showing increased baseline LDL and total cholesterol levels. The exact mechanism for this difference in lipid profiles is not exactly known, but

is thought partly to be as a result of increased peritoneal losses (30 g versus 5-8 g resulting in hypoalbuminemia) and consequently, over-production of LDL particles. This leads to increased TG levels which are also related to the deficiency in hepatic lipoprotein lipase, further aggravated by the use of glucose-based PD solutions, and their more insulin resistant state. Therefore, PD and HD participants could not be combined and analysed as a single unit for the effect of sterol-enriched margarine on serum lipid levels.

Nonetheless, in both PD and HD patients, the primary treatment should be lifestyle modification encompassing dietary habits (nutritional and behavioural changes) both prior to and in conjunction with the use of cholesterol-lowering agents. The reduction in LDL cholesterol levels should be used to assess response to therapy and adherence, but not be used as performance standards.[6,18,19] A decrease of 0.03 mmol/l LDL cholesterol is said to result in about 1-2% decrease in relative risk for CVD.[2,26] Research has also found that for each 1% reduction in serum cholesterol, there is a 2% reduction in CVD risk, and a 10% reduction in total cholesterol would decrease CVD incidence by about 30% (CDC, 2001). [2,22,26] Thus, even if the proposed decrease was not statistically significant, any decrease is shown to be beneficial in terms of reducing CVD risk. When comparing the sterol and control margarine lipid levels in both PD and HD groups, a decrease in LDL cholesterol by 3.7% (0.18 mmol/l) and 4.1% (0.08 mmol/l) for each of the respective groups was evident, showing possible clinical significance. The only problem is that not only did the LDL cholesterol decrease, but so did all the other lipid levels, including that of HDL cholesterol by 2% (0.02 mmol/l, $p=0.73$) in PD and by 14.2% (0.15 mmol/l, $p<0.01$) in HD participants. This further reduction from an already decreased baseline level in both PD and HD groups masks the cardioprotective effects seen with the reduction in LDL cholesterol. Highlighting that 'sterols' per se provide a favourable decrease in LDL cholesterol, but if not incorporated correctly within the TLC guidelines as recommended by the KDOQI and KDIGO guidelines, this benefit will not have the desired outcome.

Sterols, as part of the TLC guidelines, are said to reduce LDL cholesterol and total cholesterol in both normo- (to a lesser extent) and hypercholesterolemic individuals. The sterols inhibit dietary and biliary cholesterol absorption, as both the dietary and endogenous cholesterol becomes insoluble in the intestine (displaced from the micelles) and as a result excreted in the stool, thus reducing the number of particles being absorbed rather than the size or composition of LDL cholesterol.[5,7,20,26,32,40,43] The literature from the general population states that consuming 25 g per day (2-3 g) of sterols can reduce LDL cholesterol and total cholesterol by 0.36 mmol/l (5.9%) and 0.33 mmol/l (8.5%) respectively, using low fat sterol-enriched spreads for a medium duration of 28

days, even if an unhealthy diet is followed (not ideal).[32,42,52,55,56] In the present trial, participants included were adjusted for using '25 g/day' control and sterol-enriched margarine over a period of 8 weeks (56 days), and given a washout period of 4 weeks in between each of the trial arms. If we refer back to the AHA guidelines an 'adequate' trial of 6-12 months of following the TLC guidelines. Including the use of sterols should be considered before initiating pharmacotherapy. Which is considered an adequate trial period for observing the effectiveness of the TLC guidelines as a whole, including the use of the sterols, in lowering LDL cholesterol, as a sole or adjunct therapy to pharmacotherapy.[6,22,29] A longer trial period than the 28 days extrapolated from the general population was opted for in the present trial, to account for the complexity of the disease which may have required more time to see the desired effect. These patient groups exhibit many other risk factors associated with CVD and as a result, a multifactorial approach to treatment and duration of that treatment is important. Of which it was noted that the 56 days of trial and 28 days of washout, may still have been insufficient as the effects of the margarine (sterol or control) provided had and continued to have an effect into the washout period that followed in both the PD and HD groups. During the washout period the participants lipid levels did not reflect that which was measured at baseline, but rather the effects measured during the trial arm (control for PD and sterol for HD participants') prior to the washout period. Thus, possibly a 6-12 month trial as recommended by the AHA may have been necessary in both PD and HD groups. Because the aim was to see the effect of the 'sterol' in the margarine, and not the effect of the margarine itself; the sterol-enriched margarine lipid levels were compared to that of the control lipid levels. Thus, the effect of sterol in reducing LDL cholesterol and total cholesterol by the proposed 5.9% and 8.5% seen in the general population was more evident in the HD group with their 4.1% (0.08 mmol/l) and 7.1% (0.25 mmol/l) decrease; versus the PD group only having a 2% (0.06 mmol/l) and 3.7% (0.18 mmol/l) decrease. Not reflecting that seen in the literature, where higher initial lipid levels are associated with greater cholesterol-lowering dietary effect.[18,19] Twenty three of the PD and only 5 of the HD participants included in the trial had increased baseline lipid levels. Again, this may have been influenced by the insufficient length of trial, as lasting effects of the sterol arm of the trial had continued into the washout period (84 days) when provided first in the HD group, possibly relating to their greater reduction in LDL cholesterol and total cholesterol seen; whereas this was not possible in the PD group that were provided the sterol-enriched margarine in the second arm of the trial (56 days). This being said, some individuals have less than average response to certain treatments due to biological variability, and / or the complexity of the disease and the treatment modality received, as mentioned before, - a possible reason for our findings. Together with this, dietary intervention as a whole is complex and according to the literature, which emphasizes the effects of sterols, outlined in

the TLC guidelines, can be enhanced by consuming a low fat diet with appropriate composition of SF, trans fats, cholesterol, MUFA and PUFA within the lifestyle modification needed.[6,18,19] The latter was investigated as a possible confounding variable in the present trial.

According to the TLC guidelines extrapolated from the general population, a reduction of SF (<7%) with an isocaloric replacement with MUFA (<20%) and PUFA (<10%), negligible trans fats and 100-150 mg per day cholesterol intake as part of a low fat diet (25-35% total energy), and an increase of fibre intake (25-30 g per day, which this should provide 7-13 g per day soluble fibre) as part of the 50-60% carbohydrate intake making the diet unrefined. All of which are required to reduce not only the risk factors associated with reduced lipoprotein subclasses and particle size, but also with risk factors associated with insulin resistance, blood pressure, and increased weight – all associated with an unfavourable cardioprotective profile and evident in the complexity of the CKD patients' disease profile. Both the PD and HD participants dietary intakes assessed did not always reflect this, and varied between the 2 groups; again possibly relating to their different lipid profiles (seen in Table 18). Important to remember that possible under- and / or over-reporting could have been evident, as – due to illiteracy of most of the patients and the avoidance of possible non-compliance – a food diary was not used to evaluate their nutritional intake, but rather a 24 hour recall; which requires them to recall the previous days intake, albeit a reflection of their typical days intake. Often shown not to be accurate as it relies on their memory, and with HD participants this was a non dialysis days dietary assessment which may over estimate their dietary intake (an average of both dialysis and non dialysis days should have been assessed). The interrelationship of each of the dietary variables assessed with the effects of the sterols in changing both the PD and HD participants lipid levels will be discussed in greater detail below.

In the NHANES IV, the mean consumption of SF was 11% of total energy, as against the goal of <7% of total energy. This, too, was seen in the present trial, and could possibly influence ESRD patients' lipid profile. Saturated fat raise LDL cholesterol by decreasing LDL receptor synthesis and activity; as a result making sterols less effective as they would typically displace dietary and biliary cholesterol from these receptors, reducing the number rather than the particle size or composition being absorbed. The increased intake of SF in HD participants could be as a result of members of the medical team (nurses and doctors) advising them to consume eggs as a good source of complete protein; this together with their use of butter prior to the onset of the trial; whereas PD particpants did not show this kind of intake at baseline but as the study progressed with constant dietary counselling from the dietician the emphasis on consuming adequate protein of high biological value

to counteract their increased losses in the dialysate, may have accounted for their progressive increase in SF intake as the trial continued (still within the recommended amount specified by the TLC guidelines). Illustrating a possible reason why the PD participants' sterol use had less of a desired effect on reducing LDL cholesterol and total cholesterol levels than that seen in the HD participants'. Another important dietary aspect is that SF and trans fats should be replaced isocalorically with unsaturated fatty acids, including both MUFA and PUFA (specifically omega-3), to favourably affect plasma lipid and lipoprotein levels. This was not evident in the present trial, as SF intake increased together with PUFA and MUFA intake in the PD group; whereas in the HD group only the PUFA increased whilst MUFA, SF and cholesterol intake decreased. Eliminating SF versus increasing PUFA intake is said to be twice as effective in lowering total cholesterol levels – specifically seen in the HD group, not so much in the PD group who typically did not consume a large amount of SF in general.

Again highlighting the importance of dietary fat composition, with more MUFA and PUFA (especially omega-3 fatty acids) replacing that of SF. Saturated fat increases LDL and HDL cholesterol simultaneously, whilst PUFA, specifically omega-6 fatty acids, does the opposite.[2,3,23] Increased intake of omega-6 fatty acids are shown to exert adverse effects on the function of vascular-endothelium (reduced HDL cholesterol levels and increased LDL oxidation), or to stimulate production of proinflammatory cytokines (already present in this subgroup of patients) compromising the patients' immune status. Thus the TLC guidelines recommend a greater proportion of the PUFA intake come from omega-3 rather than omega-6 fatty acids (1:4 ratio). The reason is that omega-3 fatty acids have an anti-inflammatory property, and are thus said to be beneficial in reducing cardiovascular risk by suppressing the production of inflammatory cytokines, having antithrombotic effects (via decreased platelet aggregation), improves endothelial relaxation, decreased lipid levels (total, cholesterol, LDL cholesterol and TG) and increasing HDL cholesterol. Omega-3 fatty acids also make LDL cholesterol particles larger and as a result less atherogenic, overall inhibiting atherosclerosis. The aim is to consume 1 g per day (maximum 3 g per day) to see these benefits, while avoiding side effects associated with excess intake (increased bleeding tendency especially in patients receiving warfarin, heparin or aspirin, i.e. I HD patients; and avoid an increase in LDL cholesterol especially if TG is increased, i.e. in PD more so than in HD patients). To get the recommended amount of omega-3 fatty acids, a patient would need to consume fatty fish at least twice a week to get a better omega-3:omega-6 fatty acid ratio (1:4), which is more anti-inflammatory. The participants consumed inadequate amounts of omega-3, and an unfavourable omega-3:omega-6 ratio (1:5), possibly due to increased cost of omega-3 rich foods that are allowed on the restrictive renal diet, as cheaper sources (i.e. nuts, pilchards etc) are excluded owing to their

phosphate and potassium content. Their increased intake of especially omega-6 fatty acids (although not statistically significant), seen in both PD and HD groups, may have been as a result of including the soft tub margarine. Soft tub margarine has 40-60% PUFA (5-8% omega-6 and 1-2% omega-3), 20% SF and the remaining fat composition comes from MUFA. To avoid the deleterious effects of consuming too much omega-6 fatty acids, a maximum of 25 g per day of either the sterol-enriched or control margarine is recommended, which is in line with that which was assessed; but compared to their baseline intake thereof, this was far more than what they were typically use to consuming (especially the HD group, who prior to the study mainly consumed butter). Thus the increase in intake of omega-6 fatty acids, together with ESRD patients already being in a proinflammatory state, may make things worse. The reason why sterol-enriched margarine was included in the present trial, was because other sterol enriched foods available like juice or yoghurt are not allowed within the restrictive renal diets due to their increased potassium and phosphate content. Identifying that an alternative vector for the provision of sterols in CKD patients may have provided better results, avoiding the decrease in HDL cholesterol levels.

The literature also states that those who consume below 100 mg / 4200 kJ (1:0.02) cholesterol per day show sterol use to be less effective in reducing LDL cholesterol and total cholesterol levels due to their mechanism of action.[18] This was not seen in the present trial as both the HD (125-143 mg / 4643-5580 kJ; 1:0.03) and PD (147-170 mg / 6589-6993 kJ; 1:0.02) groups consumed greater or equal to this amount during the course of the trial. But, again showing that overall PD consumed the lower range compared to that consumed by the HD group. This, too, was seen with their overall fat intake as a percentage of total energy, whereby the HD participants consumed 113% of the mean versus the PD participants who consumed 95% of the mean. Peritoneal dialysis participants, particularly consumed a more refined carbohydrate diet together with that absorbed from the dialysate. Another dietary aspect taken into account in the TLC guidelines, whereby they recommend that not only should SF and trans fats be replaced isocalorically with unsaturated fatty acids, but also with complex carbohydrates to favourable affect plasma lipid and lipoprotein levels.

Hence the TLC guidelines emphasize the need to increase fibre intake, especially that of soluble fibre for renal patients. Fibre creates a more favourable lipid profile because of its ability to increase bile acid production and as a result decrease LDL cholesterol absorption via increased metabolism, as opposed to blocking the receptor seen with the use of sterols. The bacteria in the colon ferment the fibre to form acetate, propionate and butyrate which inhibit cholesterol synthesis.[16,17,18,22] Adequate intake thereof is associated with not only reducing LDL cholesterol levels, but is also inversely related

to CVD and blood pressure commonly seen in the complex disease process of CKD patients. Overall, both PD (more so with their greater carbohydrate intake) and HD participants' consumed inadequate amounts of fibre, 12.4 and 13.4 g per day respectively for PD and HD groups against the required 25-35 g per day. The inadequate intake of fibre could be due to fear of making the wrong selection relating to their highly restrictive diets, and / or lack of finances to purchase high fibre foods like fruit and vegetables. The inclusion of more fibre, mainly soluble fibre, is identified as another food group that may have to take centre stage in CKD patients to reduce LDL cholesterol and total cholesterol levels, without influencing HDL cholesterol levels, amongst its other benefits mentioned above. The reduced intake if fibre together with their concomitant increased intake of SF, PUFA (specifically omega-6 fatty acids) and cholesterol may have related to their less than favourable effectiveness of including plants sterols as part of their overall dietary intervention in reducing LDL cholesterol as seen in the general population.

Total energy and protein intake are other dietary variables which may relate a more cardioprotective lipid profile. The KDOQI and KDIGO guidelines recommend an intake of 30-35 kcal/kg ideal body weight in both PD and HD patients together with a protein intake of 1.2-1.3 and 1.2 g/kg ideal body weight for PD and HD patients respectively so as to avoid wasting and / or avoid obesity in CKD patients. In the HEMO study, an average of 23-27 kcal/kg ideal body weight of energy was consumed, and was evident in the present trial (under reporting may have been evident, especially with the HD group as the 24-hour recall assessed was that of a non dialysis day). Rocco et al (2005) found that 30-50% of HD patients reported an intake of <1 g/kg ideal body weight per day, which in the present trial both the PD and HD participants consumed on average 0.9 g/kg ideal body weight per day. If both total energy and protein requirements are not adequately met, not only does it negatively influence their lipid profile but are linked to an increased inflammatory state, which further negatively affects these patients' cardiac profile. Not investigated by this trial, but important to acknowledge nonetheless. Protein intake cannot be analysed in isolation but rather in combination with the required amount of total energy, as if consumed at the expense of another macronutrient, the protein will be used as a source of energy rather than to replace that lost in the dialysate, resulting in a similar finding as that with insufficient protein intake (increased protein energy malnutrition and inflammatory state). Especially important in PD patients with their greater losses, as this would result in more concomitant LDL cholesterol production. Thus if a minimum of 1.2 g/kg ideal body weight per day had been consumed a possible greater reduction in LDL cholesterol and total cholesterol may have been evident, similar to that seen in the HD group. Possible under- or over-reporting may have been evident.

Not only compliance with the diet as a whole, but also compliance with using the specified '25 g/day' may have also skewed the results slightly. A meta analysis of 41 trials showed that 2-3 g of phytosterol ester-enriched, fat based foods, like that of the margarine included in the present trial, should be consumed on a daily basis for at least 3 weeks to lower LDL cholesterol by 6-15% and total cholesterol by 9-20% in a dose-dependant manner.[16,17,18,22,23] Greater than this dose is said to not have a greater cholesterol-lowering effect as the process involved in cholesterol transport and absorption is saturable in nature.[32,42,52,55,56] Owing again to the complexity of the health status of these patients, possibly a higher dose may be needed to reflect the effects demonstrated in the general population. In the SHARP study where ESRD patients receiving RRT were given simvastatin and ezitimibe (both of which reduce endogenous cholesterol synthesis and exogenous cholesterol absorption via 2 step cholesterol homeostasis mechanisms) a reduction of only 23% was found against a 33% reduction in those not receiving RRT. The mechanisms that underlie the shift in cholesterol absorption in this patient group are not yet fully understood, but may be due to reduced hepatic clearance of transport proteins (chylomicrons and VLDL cholesterol) commonly seen in ESRD patients, or may be due to a reduction in endogenous cholesterol synthesis and a consecutive increase in cholesterol absorption that occurs to maintain homeostasis more so in HD patients with less protein losses versus PD patients.[10,11,12] Not only this, as the compliance of using the specified amount of sterol-enriched margarine was measured upon participants returning their tubs, whereby the remaining margarine was measured. If the participants' returned a 'clean' tub, even though they were instructed not to do so, this was seen as them having consumed the recommended amount, thus included in the assessment. This may have not been true, and as a result skewed the results obtained. Just as when pharmacotherapy is not taken as prescribed, a similar finding will be evident with regards to sterol use. A less than desired outcome related to an inadequate intake of sterol. As a whole, compliance with the TLC guidelines in line with that recommended using the KDOQI and KDIGO guidelines, even though not statistically significant, was not ideal, and may have influenced the less than desired effects seen with the inclusion of the sterol-enriched margarine in the present trial. Nonetheless a trend was noted in 'sterol' reducing LDL cholesterol and total cholesterol levels, but at the expense of HDL cholesterol, possibly related to the medium in which the sterol was administered. The functional food may not completely correct lipid abnormalities, but it may be used as an adjunct with the overall diet conforming to that specified by the TLC guidelines and / or pharmacotherapy.

Cholesterol-lowering medications like statins not only reduce LDL cholesterol and total cholesterol levels but have many other cardioprotective effects like decreasing biomarkers of inflammation (atherogenic lipoproteins like LDL cholesterol and CRP) and oxidative stress in a dose-related manner. The statin mainly used with the participants in this study was Simvastatin, which is a short-acting statin as opposed to the longer-acting variants, like atorvastatin, which provide up to 24-hour suppression of cholesterol biosynthesis and may give more favourable outcomes in terms of an improved cardiovascular profile. This is also because longer-acting variants are not reliant on the participant taking them regularly or at a certain time of day, where patient compliance is a confounding variable. Combination therapy is far better than doubling the dose of the statin to avoid adverse effects relating to medication side effects and, are targeted simultaneously resulting in more favourable outcomes. Several large-scale five-year trials (4D, AURORA, SHARP) involving ESRD patients found statins to be safe and to reduce CVD mortality and morbidity. An assessment of these studies led to the investigation of the individual response to dietary cholesterol intake and the current treatment modalities used to try to reduce cholesterol and LDL cholesterol levels and classify them as either hypo- or hyper-responders. Rogacev et al. came to a preliminary conclusion that ESRD patients receiving HD to be the latter, namely hyper-responders, which involved decreased basal rates of cholesterol synthesis and increased serum cholesterol levels secondary to exaggerated response to dietary cholesterol intake. This may be due to reduced hepatic clearance of chylomicrons and VLDL cholesterol or owing to decreased endogenous cholesterol synthesis secondary to enhanced cholesterol absorption so as to maintain homeostasis.[10,11,12] Which may have been evident in HD participants involved in the trial who consumed more fat (saturated fat, PUFA and cholesterol) versus PD participants who consumed this within the recommended levels specified by the TLC guidelines as indicated by the KDOQI and KDIGO guidelines thus not relating to HD participants having higher baseline total cholesterol and LDL cholesterol levels. Illustrating that even though statistically significant reductions were not seen in HD participants, a trend towards this was evident; possibly related to their diet composition favouring a more fat versus refined carbohydrate in PD participants. Thus HD patients may have greater effects of including sterols as part of a complete cardioprotective diet than PD patients related to this. Reaffirming the need for these patients' diets to conform to the KDOQI and KDIGO guidelines including that of the TLC recommendations, possibly in combination with pharmacotherapy if already initiated. This would reduce the dose required and as a result the associated side effects that commonly occur with this increased dose, particularly in those more predisposed to them, i.e. CKD patients.

The inclusion of functional foods with added plant sterols as components of a healthy lifestyle can be used as a sole or adjunct treatment modaility to reduce LDL cholesterol levels in those who have elevated levels and don't qualify for pharmacotherapy, and those receiving pharmacotherapy who do not reach their LDL cholesterol targets. Not forgetting that appropriate and aggressive lifestyle management is essential to avoid the development and progression of atherosclerosis and CVD (key preventative measures). If both diet and pharmacotherapy are combined, it is said to be more beneficial than increasing the dose of the statin alone as they use different mechanisms of action. Thus, inadequate or reduced compliance can undermine the effectiveness of both pharmacotherapy and therapeutic lifestyle regimens and should not be overlooked as possible confounding variables relating to the less than desired outcomes of sterol-enriched margarine in reducing LDL cholesterol and total cholesterol levels in this trial. Ongoing interaction and counselling with patients with chronic diseases like that of CKD, is crucial in promoting compliance. Even post counselling, the CKD patients are often afraid to eat, and receive conflicting nutrition information not only from family members but also from members of the medical team. The duration of treatment modality received, too, influences this compliance; PD participants mean duration of treatment was 4 years (1-10) , and HD participants mean duration of treatment was 6 years (1-16) seen in Table 18. If compliance is obtained, this would result in less medication being used, and as a result decrease public health cost. The challenge is to implement programmes that effectively identify ESRD patients who are at risk for vascular disease and to offer them cost-effective, greater benefit to harm interventions.

Initially, the required sample size indicated by the statistician to show statistical significance was 88 in total (44 PD and 44 HD); this number subsequently reduced to 73. Eighty-nine participants from both the HD and PD clinics met the inclusion criteria, and opted to be a part of the trial; but during the course of the trial a few passed away or were relocated to other hospitals and, as a result, the numbers slowly decreased. Some participants' blood values were contaminated or unusable, and consequently were excluded from the trial and when comparing the effects of the sterols – this was controlled for those who used the specified 25 g per day; further reducing the number of participants evaluated (n=27 and n=22 for PD and HD participants respectively). Another possible reason why the findings were not of statistical significance is that the final sample size was smaller than that initially required (RMSSE 64 and 71% for PD and HD respectively, P 0.05).

Most of the participants included in the present study were middle-aged, female, fairly active and their main underlying condition was hypertension (with a strong family history). These factors emerged when interpreting the findings. No significant impact of these potential covariates on the

absolute and relative changes in effects of sterol in lowering total and LDL cholesterol levels could be detected (P-value >0.05). In a previous meta-analysis by Law et al (2000) and Katan et al (2003), older patients (>45years for males and >55years for females) showed larger reductions in LDL cholesterol levels, possibly due to higher baseline LDL cholesterol concentrations with increasing age.[42] In the present study, the mean age for PD and HD respectively was 39 and 41 years, and 23 of the PD and 4 of the HD participants had elevated baseline LDL cholesterol and total cholesterol levels; not in line with these findings, but more in line with typical lipid profiles seen in PD and HD patients respectively as mentioned before. Majority of the participants stated that they were moderately active, which gave them a more favourable cardioprotective picture as exercise increases HDL cholesterol, increases lipoprotein lipase levels, decreases weight and increases insulin sensitivity, improves blood pressure, decreases platelet aggregation and fibrinogen and provides far better cardiac function. The question regarding the level of activity on the information document (Addendum A) may have been misinterpreted, over representing them as being active when they in actual fact were not. Most of the participants were noted to have hypertension as the cause of CKD, unlike in other countries where diabetes is the main underlying disease. Medications prescribed for hypertension, such as β-blockers are known to have adverse effects on serum lipid levels. Most of the participants in the trial received such medication to help control their blood pressure levels, especially since most of the participants were on more than 1 blood pressure agent. Increased blood pressure damages the endothelial lining of the arteries, which allows LDL cholesterol to enter in increased amounts. Highlighting the need to reduce LDL cholesterol levels in these patients who are more predisposed to their deleterious effects on cardiac health and so decrease ASCVD be it with pharmacotherapy and / or dietary lifestyle changes where benefit outweighs harm relating to intensity of therapy provided to these patients.

Dyslipidemia is directly related to an increased BMI, and adiposity is the principal nutrition-related influence found in atherogenic dyslipidemia both of which were measured in the present study. That being said, BMI does not distinguish between fat-free and fat mass; and the literature recommends that for patients receiving RRT, focus should be placed on body composition. Both PD and HD groups had normal BMI and while using the margarine, there was no significant change in the overall BMI of the participants in the study. Android obesity (reflecting visceral fat, measured with WC) modifies the effect of lipids on atherosclerosis and is a greater predictor of CVD than BMI alone, hence it is was measured to account for this, but in the case of PD patients this was not possible.[8,74,78,79,80] If it had been possible, logistically (not all patients could complete their dialysate in the clinic due to the space constraints in a busy clinic), this may have influenced the results obtained for this subgroup of

patients in being a possible confounding variable. In HD this was not the case, as their average WC was 88cm, and when separated according to gender, it remained normal. Possibly relating to their less atherogenic lipid profile whereby only 5 had increased LDL cholesterol and total cholesterol levels versus 23 in the PD group.

In summary, numerous studies in the general public have shown that the inclusion of plant sterols in the region of 2 g/day (25 g/day sterol-enriched margarine) within a four-week period achieve reductions in LDL cholesterol of 10–15%, and is considered a safe means of doing so. Similar decreases in patients with ESRD receiving RRT did not illustrate this percentage of decrease, but did show a trend towards this. The vector used to provide the sterols and their overall diet not keeping in line with that recommended by the TLC guidelines as part of the KDOQI and KDIGO guidelines is important for PD and HD participants alike in reducing LDL cholesterol and total cholesterol levels without negatively influencing HDL cholesterol levels. However, because the HDL cholesterol levels decreased in both the PD and HD groups together with the LDL cholesterol and total cholesterol, prevention of atherosclerosis may not be evident. As a result the present study findings show that sterols may reduce LDL cholesterol and total cholesterol levels, but sterol enriched margarine does not prevent or reduce atherosclerosis in PD and more so in HD participants with their significant reduction in HDL cholesterol levels.

### 5.2. LIMITATIONS OF THE STUDY

Study limitations include small sample size, inclusion of participants that at baseline did not have increased LDL cholesterol levels (form part of inclusion criteria), used a control margarine that still had an effect on the lipid profiles of participants (did not act as a placebo), inadequate duration of the individual arms of the trial (require longer than 8 weeks of trial and 4 weeks of washout), not asking HD participants dietary history on dialysis and non-dialysis days (give a true reflection of their typical dietary intake), possible under- or over-reporting in terms of dietary intake measured using a 24-hour recall (food diary), select another medium in which to provide the sterol (not a PUFA rich in omega-6 fatty acids), non-compliance in terms of using the specified 25 g/day of margarine, and non-compliance with the dietary guidelines specified according to KDOQI NCEP/ATP III guidelines (interrelates with effect of sterols).

# CHAPTER 6: CONCLUSION AND RECOMMENDATIONS

## 6.1. CONCLUSIONS

A tailored nutritional intervention according to each patient's age, diagnosis, treatment modality including pharmacological treatment, lipid levels, and other medical conditions present as indicated using the KDOQI and KDIGO guidelines is necessary. Sterols as part of a fat-modified diet may decrease total cholesterol and LDL cholesterol levels beyond statin therapy alone if a different vector is used, and if possibly a longer trial and washout period is used, and / or a different or no control is provided as this continued to increase LDL cholesterol levels above the baseline with the provision of more fat in their diet. Thus, the general use of 2–3 g of sterols as an adjunctive therapy to a diet low in total fat, saturated fat, trans fat and dietary cholesterol and moderate in MUFA and PUFA (4:1 ratio of omega-6:omega-3), as well as the use of statins in CKD patients receiving renal replacement therapy also to lower total cholesterol and LDL cholesterol levels may still be advocated in those with a more dyslipidemic serum profile like that in your PD participants, but additional research is necessary to evaluate this further.

## 6.2. RECOMMENDATIONS

Possibly only include those patients, like your PD patients, with an elevated LDL cholesterol level over a longer trial and washout period, using a more appropriate medium to include plant sterols so as to be incorporated into the patients' typical diet, and to possibly control for dietary intake by providing patients with meals to make up for their total dietary intake keeping in line with that recommended by the TLC guidelines as part of the KDOQI and KDIGO guidelines. Consider a comparative trial where we make use of Glucachol-22 (a soluble fibre isolate) versus using plant sterols to lower LDL cholesterol. Reasoning thereof is because their dietary intake of saturated fat and cholesterol was within the recommendations in both the PD and HD groups. But the intake of refined carbohydrates was notably high especially in the PD group relating to their dietary intake and glucose absorbed from the dialysate. The effect of the control margarine in PD group may have continued into the washout (LDL increased above baseline) and sterol arm (decreased slightly from baseline) of the trial.

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# ADDENDA

## Addendum A: Data extraction form

| Data Collection Form: | | | | | | | |
|---|---|---|---|---|---|---|---|
| ***Randomly Generated Patient Number:*** _____ | | | | | | | |
| Telephone Number: | | | | | | | |
| Home Language: | | | | | | | |
| Age: | | Gender: | | Race (B,W,C,I,O): | | | |
| Aetiology of CKD: | | | | | | | |
| Duration & Type RRT: | | | | | | | |
| | | | | | | | |
| Use of Cholesterol lowering agents: | | | | Y | | N | |
| If Yes which agents & for how long? | | | | | | | |
| | | | | | | | |
| **Traditional Risk Factors** | | | | | | | |
| Level of activity: | | | | | | | |
| *none; moderate = active at work; active = 3x/wk for 30-45min* | | | | | | | |
| Smoke: | | Y | | N | | | |
| | | No Yrs | | Amount | | | |
| Drink Alcohol: | | Y | | N | | | |
| How much, how often: | | | | | | | |
| Family History of CVD: | | Y | | N | | | |
| **Anthropometry** | | | | | | | |
| Dry Weight: | [1] | [2] | [3] | | | | |
| BMI: | [1] | [2] | [3] | | | | |
| Usual Weight: | | | Height: | | | | |
| Waist Circumference: | | | | | | | |
| **Biochemistry** | | | | | | | |
| S-Creatinine | [1] | [2] | [3] | | | | |
| Lipogram | | | | | | | |
| Total Cholesterol | [1] | [2] | [3] | | | | |
| LDL cholesterol | [1] | [2] | [3] | | | | |
| HDL Cholesterol | [1] | [2] | [3] | | | | |
| TG | [1] | [2] | [3] | | | | |
| **Dietary** | | | | | | | |
| Quantity of margarine used per day? | | | | | | | |
| Tubs returned, & amount left over? | | | | | | | |

24Hr Recall (1):

| Food | Time | Amount |
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24Hr Recall (2):

| Food | Time | Amount |
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24Hr Recall (3):

| Food | Time | Amount |
|---|---|---|
| | | |
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**Addendum B: English consent form**

# PARTICIPANT INFORMATION LEAFLET AND CONSENT FORM

**TITLE OF THE RESEARCH PROJECT:**
A cross-over randomised controlled trial to determine whether end stage renal disease patients receiving chronic renal replacement therapy are more likely to have an improve lipid profile after including plant sterols as part of their dietary intake for four weeks.

REFERENCE NUMBER:

PRINCIPAL INVESTIGATOR: Mrs Ribeiro

ADDRESS: 9 Jubilee Road
Parktown West
JHB
2000

CONTACT NUMBER: (011) 488-4348

You are being invited to take part in a research project. Please take some time to read the information presented here, which will explain the details of this project. Please ask the study staff or dietician any questions about any part of this project that you do not fully understand. It is very important that you are fully satisfied that you clearly understand what this research entails and how you could be involved. Also, your participation is entirely voluntary and you are free to decline to participate. If you say no, this will not affect you negatively in any way whatsoever. You are also free to withdraw from the study at any point, even if you do agree to take part.

This study has been approved by the Health Research Ethics Committee at Stellenbosch University and The University of the Witwatersrand, and will be conducted according to the ethical guidelines and principles of the international Declaration of Helsinki, South African Guidelines for Good Clinical Practice and the Medical Research Council (MRC) Ethical Guidelines for Research.

**1. What is this research study all about?**

- The study will be conducted at CMJAH, whereby 44 Hemodialysis and 44 Peritoneal dialysis patients will be included in the study. Thus altogether 88 patients will be recruited from CMJAH.
- The purpose of this project is to study the effect of phytosterol-enriched margarine on reducing serum cholesterol levels and thus reducing the incidence of Cardiovascular Disease. Your medical information will be used to see what factors may affect the development of abnormal cholesterol levels and as a result increase the risk for Cardiovascular Disease. From the information collected and studied in this project I hope to learn more about this product in reducing cholesterol levels and as a result reducing Cardiovascular Disease.
- With your permission, I would like to collect health information about you, including information about your general health (height, weight, waist circumference, results from blood tests, medications) related to medical treatments and care you receive; and a finger prick blood sample will be collected. I would like to collect this information about you once a month (every 4 weeks) for 3 consecutive months whilst attending the clinics at CMJAH. This study does not involve any treatment; just the collection and study of medical information.
- Participants will be randomly provided with the enriched margarine or a standard margarine for 1 month in the 3 month period. For the other 2 months a standard margarine will be provided. Both the dietician and the participants will not know which product is being used.

**2. Why have you been invited to participate?**

- Patients with end stage renal disease receiving hemodialysis or peritoneal dialysis are considered a secondary cause for abnormal lipid (fat) levels. Plant sterols have been used as part of patients with no end stage renal disease dietary intake to improve their lipid levels. Thus this study would like to see whether or not it will have the same effect in those with end stage renal disease. Only if you have given informed consent, will you be able to participate in the study.

**3. What will your responsibilities be?**

- Your participation in this study will not require more time from you other than for the initial visit where this study is explained to you. If you agree to participate, your medical information will be collected from your medical record after each visit, and the nurse will obtain a finger prick blood sample from you. This is the only direct participation we will need

from you other than you following the renal diet as prescribed by your dietician and consuming the allocated margarine in the correct proportions as indicated by your dietician.

**4. Will you benefit from taking part in this research?**

- Possible benefits from participating in this study are that your overall nutritional status may be enhanced with an increase in energy intake and an increased interaction with the dietician.
- Another possible benefit is that the outcome of the study will improve the nutritional treatment of current and future patients with end stage renal disease receiving hemodialysis or peritoneal dialysis.

**5. Are there in risks involved in your taking part in this research?**

- There will be a slight increase in the number of blood tests to be undergone (finger prick test for lipid profile). Thus additional discomfort by drawing blood samples can be brought upon yourself, resulting in slight bruising or redness and you may feel that it is slightly painful. This will be minimized by using correct blood sampling techniques by one registered dietician or nurse throughout the study.

**6. If you do not agree to take part, what alternatives do you have?**

- If you do not consent to participate in the study, standard treatment will be provided to you.

**7. Who will have access to your medical records?**

- Information relating to the treatment and care you receive such as blood tests, physical examination results (weight, height and waist circumference) and medications will be used. This information will be treated as confidential and protected. Your identity will not be disclosed in any published and written material resulting from the study.
- The following parties are authorized to use and/ or disclose your health information in connection with the research study:
    - The protocol director
    - Any unit at Stellenbosch University and the University of the Witwatersrand
    - Research staff working on this project

**8. Will you be paid to take part in this study and are there any costs involved?**

- No but the margarines to be used will be provided by the research director (dietician) and the blood tests will not be charged for, if you do take part in the study.

**9. Is there anything else that you should know or do?**

- You should inform your family practitioner or usual doctor that you are taking part in a research study.
- You can contact Nicole (dietician) at tel (011) 488-4348 if you have any further queries or encounter any problems.
- You can contact the Health Research Ethics Committee at 021-938 9207 if you have any concerns or complaints that have not been adequately addressed by your study dietician.
- You will receive a copy of this information and consent form for your own records.

**10. Declaration by participant**

By signing below, I …….. agree to take part in a research study entitled 'A cross-over randomised controlled trial to determine whether end stage renal disease patients receiving chronic renal replacement therapy are more likely to have an improve lipid profile after including plant sterols as part of their dietary intake for four weeks.'

**I declare that:**

- I have read or had read to me this information and consent form and it is written in a language with which I am fluent and comfortable.
- I have had a chance to ask questions and all my questions have been adequately answered.
- I understand that taking part in this study is **voluntary** and I have not been pressurised to take part.
- I may choose to leave the study at any time and will not be penalised or prejudiced in any way.
- I may be asked to leave the study before it has finished, if the study doctor or researcher feels it is in my best interests, or if I do not follow the study plan, as agreed to.

Signed at (*place*) ..... on (*date*) …….. 2013.

**Signature of participant** **Signature of witness**

**11. Declaration by investigator**

I *(name)* …… declare that:

- I explained the information in this document to ……..
- I encouraged him/her to ask questions and took adequate time to answer them.
- I am satisfied that he/she adequately understands all aspects of the research, as discussed above
- I did/did not use an interpreter. (*Interpreter signature below).*

Signed at (*place*) ..... on (*date*) ……..…….. 2013.

**Signature of investigator** **Signature of witness**

**12. Declaration by interpreter**

I *(name)* …… declare that:

- I assisted the investigator Nicole to explain the information in this document to (*name of participant*) …….. using the language medium of …….
- We encouraged him/her to ask questions and took adequate time to answer them.
- I conveyed a factually correct version of what was related to me.
- I am satisfied that the participant fully understands the content of this informed consent document and has had all his/her question satisfactorily answered.

Signed at (*place*) ..... on ……..2013

**Signature of interpreter** **Signature of witness**

**Addendum C: Ethics approval**

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M130765

| | |
|---|---|
| **NAME: (Principal Investigator)** | Ms Nicole P Ribeiro |
| **DEPARTMENT:** | Department of Nephrology<br>CM Johannesburg Academic Hospital |
| **PROJECT TITLE:** | A Cross-Over Randomised Controlled Trial to determine Whether End Stage Renal Disease Patients Receiving Chronic Renal Replacement Therapy Are more Likely to Have improved Lipid Profile after Includuing Plant Sterols as... |
| **DATE CONSIDERED:** | 26/07/2013 |
| **DECISION:** | Approved unconditionally |
| **CONDITIONS:** | |
| **SUPERVISOR:** | Prof S Naicker |
| **APPROVED BY:** | Professor PE Cleaton-Jones, Chairperson, HREC (Medical) |

**DATE OF APPROVAL:** 29/07/2013

**This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.**

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.
I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report.**

Principal Investigator Signature M130765Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

UNIVERSITEIT·STELLENBOSCH·UNIVERSITY
jou kennisvennoot · your knowledge partner

# Approval Notice
## Response to Modifications- (New Application)

18-Apr-2013
RIBEIRO, Nicole Pereira

**Ethics Refernce #:** S12/11/291

**Title:** **A cross-over randomized controlled trial to determine whether end stage renal disease patients receiving chronic renal replacement therapy are more likely to have an improved lipid profile after including plant sterols as part of their dietary intake for four weeks**

Dear Ms Nicole RIBEIRO,

**The Response to Modifications -** ***(New Application)*** **received on 25-Mar-2013, was reviewed by members of Health Research Ethics Committee 2 via Expedited review procedures on 10-Apr-2013 and was approved.**
Please note the following information about your approved research protocol:

Protocol Approval Period: **10-Apr-2013 -10-Apr-2014**

Please remember to use your **protocol number** (S12/11/291) on any documents or correspondence with the HREC concerning your research protocol.

Please note that the HREC has the prerogative and authority to ask further questions, seek additional information, require further modifications, or monitor the conduct of your research and the consent process.

**After Ethical Review:**
Please note a template of the progress report is obtainable on www.sun.ac.za/rds and should be submitted to the Committee before the year has expired.
The Committee will then consider the continuation of the project for a further year (if necessary). Annually a number of projects may be selected randomly for an external audit.
Translation of the consent document to the language applicable to the study participants should be submitted.

Federal Wide Assurance Number: 00001372
Institutional Review Board (IRB) Number: IRB0005239

The Health Research Ethics Committee complies with the SA National Health Act No.61 2003 as it pertains to health research and the United States Code of Federal Regulations Title 45 Part 46. This committee abides by the ethical norms and principles for research, established by the Declaration of Helsinki, the South African Medical Research Council Guidelines as well as the Guidelines for Ethical Research: Principles Structures and Processes 2004 (Department of Health).

**Provincial and City of Cape Town Approval**

Please note that for research at a primary or secondary healthcare facility permission must still be obtained from the relevant authorities (Western Cape Department of Health and/or City Health) to conduct the research as stated in the protocol. Contact persons are Ms Claudette Abrahams at Western Cape Department of Health (healthres@pgwc.gov.za Tel: +27 21 483 9907) and Dr Helene Visser at City Health (Helene.Visser@capetown.gov.za Tel: +27 21 400 3981). Research that will be conducted at any tertiary academic institution requires approval from the relevant hospital manager. Ethics approval is required BEFORE approval can be obtained from these health authorities.

We wish you the best as you conduct your research.
For standard HREC forms and documents please visit: www.sun.ac.za/rds

If you have any questions or need further assistance, please contact the HREC office at 0219389207.

**Included Documents:**
Protocol and Consent
Checklist
CVs
Package Insert
Declaration
Cover letter
Synopsis
Certificate of Insurance
Application form

## Addendum D: References tables for methods section

**Table 19:** Fiftieth (50th) Percentile of Standard Body Weight for Men and Women

**Fiftieth (50th) Percentile of Standard Body Weight for Men**

| Age | 25–54 years | | | 55–74 years | | |
|---|---|---|---|---|---|---|
| | Weight (kg) | | | | | |
| Height (cm) | Small frame | Medium frame | Large frame | Small frame | Medium frame | Large frame |
| 157 | 64 | 68 | 82 | 61 | 68 | 77 |
| 160 | 61 | 71 | 83 | 62 | 70 | 80 |
| 163 | 66 | 71 | 84 | 63 | 71 | 77 |
| 165 | 66 | 74 | 79 | 70 | 72 | 79 |
| 168 | 67 | 75 | 84 | 68 | 74 | 80 |
| 170 | 71 | 77 | 84 | 69 | 78 | 85 |
| 173 | 71 | 78 | 86 | 70 | 78 | 83 |
| 175 | 74 | 78 | 89 | 75 | 77 | 84 |
| 178 | 75 | 81 | 87 | 76 | 80 | 87 |
| 180 | 76 | 81 | 91 | 69 | 84 | 84 |
| 183 | 74 | 84 | 91 | 76[a] | 81 | 90 |
| 185 | 79 | 85 | 93 | 78[a] | 88 | 88 |
| 188 | 80 | 88 | 92 | 77[a] | 95 | 89 |

**Fifthieth (50th) Percentile of Standard Body Weight for Women**

| Age | 25–54 years | | | 55–74 years | | |
|---|---|---|---|---|---|---|
| | Weight (kg) | | | | | |
| Height (cm) | Small frame | Medium frame | Large frame | Small frame | Medium frame | Large frame |
| 147 | 52 | 63 | 86[a] | 54 | 57 | 92 |
| 150 | 53 | 66 | 78 | 55 | 62 | 78 |
| 152 | 53 | 60 | 87 | 54 | 65 | 78 |
| 155 | 54 | 61 | 81 | 56 | 64 | 79 |
| 157 | 55 | 61 | 81 | 58 | 64 | 82 |
| 160 | 55 | 62 | 83 | 58 | 65 | 80 |
| 163 | 57 | 62 | 79 | 60 | 66 | 77 |
| 165 | 60 | 63 | 81 | 60 | 67 | 80 |
| 168 | 58 | 63 | 75 | 68 | 66 | 82 |
| 170 | 59 | 65 | 80 | 61[a] | 72 | 80 |
| 173 | 62 | 67 | 76 | 61[a] | 70 | 79 |
| 175 | 63* | 68 | 79 | 62[a] | 72[a] | 85[a] |
| 178 | 64* | 70 | 76 | 63[a] | 73[a] | 85[a] |

[a]*Value estimated through linear regression equation.*
*(NHANES I and II); reproduced with permission from Frisancho et al. The American Journal of Clinical Nutrition*

**Table 20:** Macronutrient Requirements for patients receiving RRT

| | CRF | CRF |
|---|---|---|
| | HD | CAPD |
| Protein | 1.2g/kg | 1.2-1.3g/kg |
| Energy | <60years: 35kcal/kg (include dialysate from PD) | |
| | >60years: 30-35kcal/kg (include dialysate from PD) | |
| Fat | 30-40%TE (closer to 30% optimal) | |
| | <300mg/d Cholesterol | |
| | SF:PUFA:MUFA <10:<10:>10% | |
| Carbohydrate | 50-60% TE (including that from dialysate in PD patients (Table 4) | |
| Fibre | 20-25g/d | |

*(NFK 2002, K/DOQI 2000, Makoff 1999, Mitch & Klahr 1998)*

**Table 21:** Therapeutic Lifestyle Change for Adults with ESRD[10]

| ATP III Nutritional Components of the TLC Diet | |
|---|---|
| Nutrient | Daily Recommended Intake |
| Total Fat | 25 - 35% of total kilocalories |
| Saturated Fat | <7% of total kilocalories |
| Polyunsaturated Fat | Up to 10% of total calories |
| Monounsaturated Fat | Up to 20% of total calories |
| Cholesterol | <200mg |
| Carbohydrate (esp. complex) | 50 - 60% of total kilocalories |
| Therapeutic Options for LDL lowering | |
| Daily Fibre intake | 20 - 30g |
| Emphasize Soluble Fibre | 5-10g |
| Plant stanols/sterols | 2g/day |

**Table 22:** Concentration of dextrose absorbed, to be excluded from Carbohydrate requirements calculated in PD patients[26]

| Dialysate Dextrose Concentration | Grams of Dextrose/L | kcal/L from Dextrose | kcal/L with CAPD (60%)* |
|---|---|---|---|
| 1.50% | 15g | 51kcal | 31kcal |
| 2.50% | 25g | 85kcal | 51kcal |
| 4.25% | 42.5g | 144.5kcal | 86.7kcal |

**60% dextrose absorbed with CAPD*

***each gram of dextrose = 3.4kcal*

*E.g. Energy/L x Total Volume*